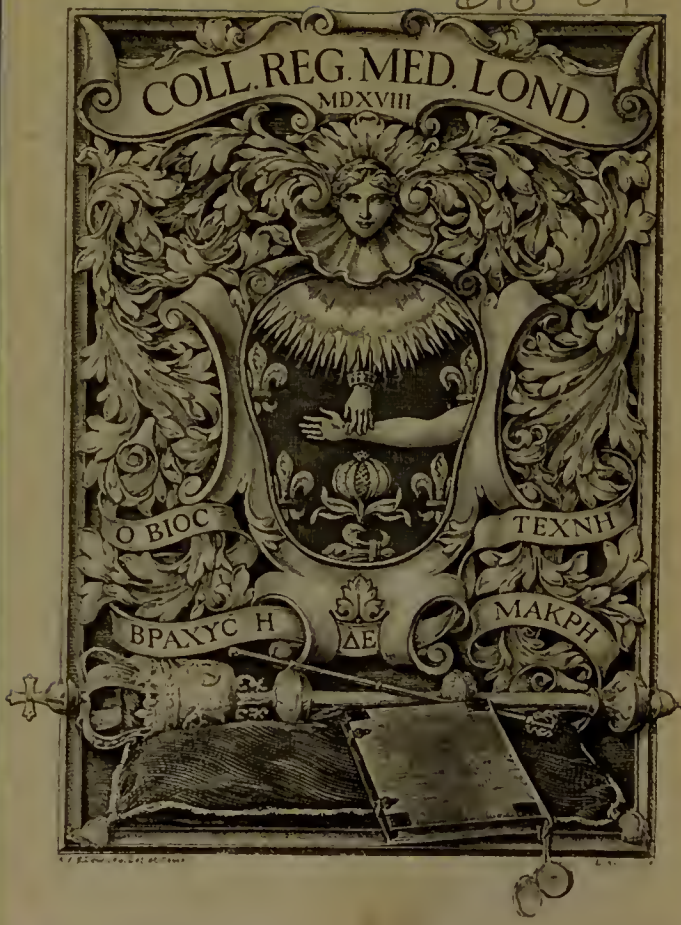
AIDS TO PATHOLOGY



Clifford Gale Laing.
Owens College
Manchester
1909.

AIDS TO PATHOLOGY

AIDS

TO

PATHOLOGY

BY

HARRY CAMPBELL, M.D. LOND.

BACHELOR OF SURGERY AND FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS, LONDON; LECTURER AT THE POLYCLINIC; SENIOR PHYSICIAN, NORTH-WEST LONDON HOSPITAL; PHYSICIAN, WEST END HOSPITAL FOR NERVOUS DISEASES; LATE PATHOLOGIST AT THE NORTH-WEST LONDON HOSPITAL

LONDON
BAILLIÈRE TINDALL & COX
8, HENRIETTA STREET, COVENT GARDEN
1908

...mours.

...ucoma (L)

...coma.

...ugin

Specific

T.B.

Typhoid

Sy (Rectum)

Dif. (")

Anthrax (S)

Actinomycosis

Dysentery (L)

Non Specific

Dip. (L)

Catarrh

Haemorrhage.

Uraemia (L?)

Stercoral (L)

Simple Food.

Corrosives.

Toxic by Excretion

Embolic.

Traumatic.

Phlegmonous

Syphilis.

Ulc. Colitis (L)

Necrosis due to obstruction

81

Multiple Ulcers

Typhoid

T.B.

Dysentery } L.I. only.

Ulc. Colitis }

Follicular }

...ular Ulcers

Malignant growth

T.B.

PREFACE

I HAVE endeavoured in the following pages to present concisely, and as briefly as possible, the known facts of Pathology.

There is no pretence to a complete or exhaustive treatment of the subject. The student must regard the description of each disease as a framework into which he can fit all the information acquired from the post-mortem room, the museum, and the laboratory.

It is hoped that the section on 'Immunity and Opsonins' may help to elucidate a somewhat difficult problem in serum-therapeutics.

H. C.

23, WIMPOLE STREET,
CAVENDISH SQUARE, W.,
November, 1907.

CONTENTS

AIDS TO PATHOLOGY

'By the *cause* of an event we mean the circumstances which must have preceded in order that the event should happen. Nor is it generally possible to say that an event has one single cause and no more. There are usually many different things, conditions, or circumstances necessary to the production of an effect, and all of them must he considered causes, or necessary parts of the cause.'—JEVONS.

THE CELL.

THE organic unit is the cell, and it bears the same relation to the body that the brick bears to the house. It is composed of a sponge-like mass, the *spongioplasm*, soaked in lymph, the *hyaloplasm*, and in most cases possesses a limiting membrane (the cell wall), a nucleus, and nucleoli.

The cells lie bathed in lymph, which, though at times tending to stagnate locally, as in the muscles during rest, may be regarded as more or less continually on the flux.

The *lymph-flow* to the cell carries the oxygen, proteids, carbohydrates, fats, salts, and other substances necessary for the bio-chemical changes that are constantly taking place; the *lymph-ebb* carries away from the cell its waste products, such as carbonic acid and ammonia.

THE BLOOD AND ITS DISEASES.

The blood consists of a fluid—the plasma—in which float the blood-corpuscles.

The **plasma** contains, besides its waste products, nutrient proteids, carbohydrates, fats, and salts, as well as a multiplicity of other less understood substances necessary to normal nutrition, such as hormones and ferments. It is continually oozing through the thin walls of the capillaries to replenish the lymph.

The **lymph**, which is a *dilute* plasma, is the medium of exchange between the blood and the tissues, conveying food to the latter, and taking from them waste products. It provides the cells of the body with a saline medium similar to that inhabited by their far-off amœboid ocean ancestors.

The blood-corpuscles are of three kinds:

(*a*) The coloured, called **chromocytes** (or erythrocytes);
(*b*) The colourless, called **leucocytes**;
(*c*) The **blood-platelets**.

The Chromocytes (Erythrocytes).

The chromocytes of all mammals in health are non-nucleated (except in embryonic life). Although authorities differ, the general consensus of opinion is that in health their numbers approximately are 5,000,000 per cubic millimetre in man, 4,500,000 per cubic millimetre in woman. Their average diameter is 7·5 μ ($\frac{1}{3500}$ inch), and in health does not vary more than 1 μ in extent. (The Greek letter μ = a micromillimetre = $\frac{1}{1000}$ part of a millimetre = $\frac{1}{25000}$ inch.)

Such influences as food, pregnancy, and lactation have but slight influence on their number during health, but living in high altitudes may cause an increase. An augmentation to the extent of 2,000,000 per cubic millimetre has been observed at a height of 6,000 feet above the sea-level. A similar increase has been observed in the cyanosis of congenital heart disease and in mitral stenosis.

Source.—The nucleated red cells (hæmatoblasts) of the bone-marrow.

Abnormal Chromocytes.

Non-nucleated	Microcytes. Megalocytes. Poikilocytes.
Nucleated, or erythroblasts	Normoblasts. Megaloblasts. Microblasts.

Microcytes (or small chromocytes) vary in diameter from 3 μ to 6 μ. They are found in most kinds of anæmia.

Megalocytes (or large chromocytes) vary in diameter from 8 μ to 16 μ. They are found typically in pernicious anæmia, but they may be present in any kind of severe anæmia.

Poikilocytes (oval, pear-shaped, or fiddle-shaped chromocytes) are present in many varieties of anæmia.

Erythroblasts (or nucleated chromocytes) only display their nuclei when stained. Nucleated red blood cells are present during intra-uterine life, but are never seen in healthy blood after birth. They are found especially in

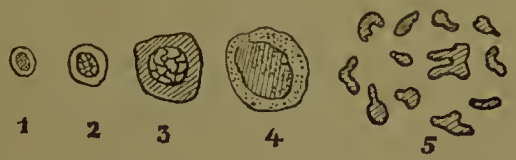


FIG. 1.—ABNORMAL BLOOD CELLS (DIAGRAMMATIC).
1, Microblast; 2, normoblast; 3, megaloblast; 4, myelocyte; 5, poikilocytes.

pernicious anæmia, but they may occur in any severe kind of anæmia. They are of three varieties, according to their size:

1. **Normoblasts**, of the same size as the normal chromocytes. The nucleus is rendered conspicuous by nuclear stains. They are often abundant in pernicious anæmia.

2. **Megaloblasts**, of greater size, and even double that of the normal chromocytes (10 μ to 16 μ in diameter). The nucleus, which may occupy two-thirds of the cell, stains faintly with the nuclear dyes. Megaloblasts occur almost exclusively in pernicious anæmia.

3. **Microblasts**, which are the small nucleated chromocytes. They are found in all forms of anæmia, and are of but little diagnostic importance.

Colour Index—Estimate of the Amount of Hæmoglobin.

Decrease in the number of the chromocytes, and decrease in the amount of hæmoglobin, in the blood do not neces-

sarily go hand-in-hand. The severity of most anæmias is better estimated by the deficieney of hæmoglobin than by the number of ehromoeytes; for example, in ehlorosis the number of ehromoeytes may be but little, if at all, diminished, while the amount of hæmoglobin in eaeh individual ehromocyte may be mueh redueed.

The amount of hæmoglobin (Hb) in eaeh individual chromocyte (C) is called the eolour-index. It is the ratio of the hæmoglobin pereentage to the eorpuscle percentage.

The colour-index is obtained by the use of the formula

$$\frac{o/c\ Hb}{o/c\ C}.$$

Percentage of Chromocytes.	Percentage of Hæmoglobin.	Colour-Index.
In health - 100	100	$\frac{100}{100}$, or 1
In chlorosis - 60	30	$\frac{30}{60}$, or 0·5
In pernicious anæmia - 20	30	$\frac{30}{20}$, or 1·5

Leucocytes.

In fœtal life the leucoeytes make their appearance later than the ehromoeytes.

In normal blood the proportion of leueocytes averages from 7,000 to 8,000 per cubic millimetre, their ratio to the ehromoeytes being then as 1 to 600 or 700.

In health the following kinds of leucoeytes are found:

The small lymphocytes	=22 to 25 per cent.
The large lymphocytes	= 2 to 4 per cent.
The polymorphonuclears	=70 to 72 per cent.
The eosinophiles	= 2 to 4 per cent.
Mast cells	= 0·5 per cent.

—Ehrlich.

The **small lymphocyte**, 6 μ to 8 μ in diameter. It contains a large, spherieal, deeply-staining nueleus, which occupies almost the entire eell. It is non-amœboid and non-phagoeytic, and constitutes 22 to 25 per cent. of the total leueoeytes. Souree: All lymphoid tissue.

The **large lymphocyte**, also termed hyaline (the

macrophage of Metchnikoff), 9 μ to 15 μ in diameter. Its nucleus stains less intensely than that of the small lymphocyte. It is amœboid and phagocytic, and constitutes from 2 to 4 per cent. of the total leucocytes. *Source:* The small lymphocyte.

Transitional forms between (1) and (2).

The **polymorphonuclear**, also termed neutrophile (the microphage of Metchnikoff), 9 μ to 12 μ in diameter. The nucleus stains deeply, and may assume, as its name implies, a variety of different shapes, such as lobulated, horse-shoe, or twisted like the letters S or Z. It is both amœboid and phagocytic, and by far the most numerous of all the leucocytes, constituting from 70 to 72 per cent. of the total. Pus cells consist almost entirely of the polymorphonuclear leucocytes. In leucocytosis they generally form the preponderating element. *Source:* Bone-marrow.

The **eosinophile**, 10 μ in diameter, so-called because

FIG. 2.—NORMAL LEUCOCYTES (DIAGRAMMATIC).

1, Small lymphocyte; 2, large lymphocyte; 3, polymorphonuclear; 4, eosinophile.

the large, coarse, refractile granules which it contains stain readily with eosin. The nucleus stains faintly with the basic dyes. It is amœboid, but probably not phagocytic, and constitutes from 2 to 4 per cent. of the total leucocytes. *Source:* Bone-marrow.

Mast cell (basophile), 20 μ in diameter, and containing irregular nuclei, which stain feebly. The protoplasm resembles that of the eosinophile in containing coarse basophile granules. It constitutes about 0·5 per cent. of the total leucocytes. *Source:* Bone-marrow.

Myelocytes, or Marrow Cells.

Myelocytes are cells which are normally found in bone-marrow, but are never present in healthy blood. They measure from 10 μ to 20 μ in diameter, and have a large

but feebly staining nucleus. They differ from the large lymphocytes in containing a fine granular protoplasm. They are numerous in but one disease, *i.e.*, spleno-medullary leukæmia, in which they may constitute from 30 to 60 per cent. of the total number of leucocytes.

Leucocytosis.

By this term is meant an increase in the total number of leucocytes in the blood. Any number over 10,000 per cubic millimetre may be regarded as constituting leucocytosis, so long as the increase lasts sufficiently long. (A physiological leucocytosis occurs from three to four hours after every meal, when the leucocytes may reach from 10,000 to 12,000 per cubic millimetre, but this soon passes off.) Leucocytosis is natural in pregnancy and childhood (lymphocytosis).

The presence or absence of leucocytosis may be of material aid in forming a differential diagnosis, as, for example, between pleural effusion and empyema, a leucocytosis reaching to 20,000 per cubic millimetre being indicative of the latter; again, a leucocytosis of 20,000 per cubic millimetre has led to the detection of an hepatic abscess or a pyosalpinx as against the diagnosis of enteric fever.

Leucocytosis occurs in the following diseases:

Suppuration, most fevers (except enteric, Malta fever, influenza, acute miliary tuberculosis), and malignant growths (if large).

Rickets
Scurvy
Syphilis
Whooping-cough
Acute mania
} Lymphocytosis (*i.e.*, an increase in the lymphocytes).

Asthma
Emphysema
Certain skin diseases —*e.g.*, pemphigus
Trichinosis
Ankylostomiasis
Bilharzia hæmatobia
} Eosinophilia (*i.e.*, an increase in the eosinophiles).

'All neoplasms accompanied with an increase of leucocytes are of a malignant nature' (Hayem).

Leucopenia.

This term indicates a decrease in the number of leucocytes. It occurs in the later stages of enteric, pneumonia (if fatal), and pernicious anæmia.

Anæmia.

'Anæmia' is a comprehensive term, and embraces three conditions:

Oligæmia = a decrease in the total quantity of blood.
Oligocythæmia = a decrease in the number of chromocytes.
Oligochromæmia = a decrease in the amount of hæmoglobin.

These may occur separately or together.

The normal chromocytes, born in the red marrow of bone (hæmatoblasts), live for a few weeks only and then die of senile decay.

It is obvious that an anæmia may result either from *defective blood formation* or from *excessive blood destruction*. These two factors often co-operate.

Anæmias are generally associated with a diluted condition of the plasma.

Chlorosis.

Chlorosis is probably due to defective blood formation, and affects young women chiefly. Want of fresh air and sunlight, deficient exercise, unsuitable feeding occurring at the most critical epoch in a woman's life (puberty and early womanhood), would appear to be the most important causes. Von Noorden attributes the disease to some abnormality in the internal secretion of the ovary.

Blood Changes.—The specific gravity of the plasma is unaltered. The outstanding feature of the disease is that the hæmoglobin-index is less than 1—*i.e.*, the amount of hæmoglobin in the individual chromocyte is below the normal standard.

The plasma is increased in amount, *the volume of blood being greater than in health.* Although the number of chromocytes per cubic millimetre is generally reduced (sometimes to as few as 2,000,000), their entire number

must be increased, because, as Lorrain Smith has shown, the total quantity of hæmoglobin in the blood is normal in amount.

Microcytes and poikilocytes are often present, and in severe cases megalocytes, normoblasts, and even megaloblasts.

The leucocytes are unchanged, and there is no leucocytosis.

Complications.—Œdema, venous thrombosis, fatty degeneration, visceral inflammations, optic neuritis.

Pernicious Anæmia.

Pernicious anæmia is probably due to excessive blood destruction. This conclusion is arrived at from the fact that there is a deposition of an iron-containing pigment —a product of disintegrated hæmoglobin—in the liver, spleen, and kidneys.

The cause is unknown; it is probably a toxin, perhaps developed in the alimentary tract. Very similar symptoms may occur in connection with *Ankylostomum duodenale* and *Dibothriocephalus latus*.

Blood Changes.—Specific gravity is lower than normal; the *chromocytes* are much reduced in number. When the case first comes under observation they may number only 2,000,000, and towards the end may sink to 500,000, per cubic millimetre. In a case of Quincke's they were only 143,000 per cubic millimetre. Under treatment periods of temporary improvement may occur.

Relatively the hæmoglobin is increased, so that the hæmoglobin index is greater than 1.

Microcytes, poikilocytes, and megalocytes are plentiful.

Erythroblasts (both normoblasts and megaloblasts) are usually, though not constantly, present.

Leucocytes.—As a rule there is leucopenia, the number of leucocytes in some cases being as low as 1,000 per cubic millimetre.

Hæmosiderin (or iron-containing pigment) is found in the liver, spleen, and kidneys.

Bloodvessels.—There is a great tendency to hæmorrhages in the skin, retina, brain, uterus, and serous membranes.

Bone-Marrow.—The yellow marrow of the long bones reverts to the fœtal state—*i.e.*, is transformed into a lymphoid tissue containing a large number of red nucleated cells and megaloblasts.

Viscera.—Fatty degeneration of the heart always occurs, and as a rule of the liver and kidneys also.

Nervous System.—Sclerosis of the posterior columns of the cord may be present.

Splenic Anæmia.

This disease is characterized by a great enlargement of the spleen, and progressive anæmia of the chlorotic type; no leucocytosis, and the lymphatic glands are not enlarged.

The chromocytes are diminished in number, frequently falling to 2,500,000 per cubic millimetre and occasionally to a smaller number.

The hæmoglobin index is considerably below the normal.

The enlargement of the spleen is uniform, and may be considerable; there is great increase of the stroma, and the Malpighian bodies are transformed into fibrous tissue.

Banti's Disease.

This is the combination of splenic anæmia with definite cirrhosis of the liver.

Leukæmia (Leucocythæmia).

Leukæmia is a disease characterized by an enormous and persistent increase in the number of leucocytes as the result of pathological changes in the spleen, bone-marrow, or lymphatic glands, or in any two or in all three of these. Hughes Bennett, in 1845, first drew attention to it, describing his case as one of 'suppuration of the blood.' Later in the same year, Virchow recorded a similar case, and gave the disease its present name (*leukos*, white, and *haima*, blood).

Two chief forms are recognized—the spleno-medullary and the lymphatic.

Spleno-Medullary Leukæmia.

This affection takes its name from the fact that it is associated with marked changes in the spleen and bone-marrow.

The **spleen** increases enormously, and may weigh 18 pounds. It is often adherent to the surrounding viscera. On section it is pale, the splenic pulp and fibrous stroma are seen to be greatly increased, and the Malpighian bodies are indistinct. Myelocytes, mast cells, and polymorphonuclears are plentiful in its substance.

The **bone-marrow** is hypertrophied and of increased vascularity; it contains an excess of myelocytes.

The blood is sometimes merely pale, at others it looks like a mixture of blood and pus, and in extreme cases it resembles pus. The specific gravity is generally ~~below~~ increased the normal.

The leucocytes are enormously increased, and may number from 100,000 to 500,000 per cubic millimetre in typical cases, but this number is liable to fluctuate from time to time.

Very characteristic is the presence of *myelocytes* (marrow cells), which, as a rule, constitute from 30 to 60 per cent. of all the leucocytes present.

The *eosinophiles* are generally increased in number, while the *chromocytes* are usually diminished. *Nucleated chromocytes* (erythroblasts) are a constant feature at some stage or other of the disease.

Charcot-Leyden crystals are sometimes found in the blood after its removal from the body. They are polyhedral in shape, and are probably a crystalloid product of either the plasma or the leucocytes.

Lymphatic Leukæmia.

This form of leukæmia is associated with enlargement of the lymphatic glands throughout the body. They may attain the size of walnuts. The spleen is also generally enlarged, though only moderately. This variety is much rarer than the spleno-medullary, and runs a more acute course.

The *leucocytes* are increased in number, but not to

the same extent as in spleno-medullary leukæmia, their numbers varying between 50,000 and 250,000 per cubic millimetre. The increase is due almost entirely to the presence of the *small lymphocytes*, which may constitute from 95 to 98 per cent. of all forms of leucocytes present.

The *chromocytes* are nearly always decreased in number.

Acute Leukæmia.

This is a very rare disease, and runs a fatal course within a few weeks or months. It may be either of the spleno-medullary or lymphatic type, more commonly the latter. The leucocytosis rarely exceeds 100,000 per cubic millimetre, the increase affecting principally the small lymphocytes. The chromocytes are usually diminished in number.

Hodgkin's Disease (Lymphadenoma, Lympho-Sarcoma, Pseudo-Leukæmia).

This disease also is characterized by an enlargement of the lymphatic glands throughout the body, with which are usually associated an increase of the lymphoid tissue in the tonsils, pharynx, and intestines, and the development of lymphoid masses in the liver, spleen, and kidneys. It generally starts in a single group of glands (most often the cervical or axillary), and gradually implicates the other groups.

The Blood.—At the commencement of the disease the blood is normal; later on, anæmia of the chlorotic type may appear. There is no leucocytosis, except that towards the end there may be a moderate increase of the polymorpho nuclears.

This negative character of the blood is of value in differentiating the disease from leukæmia.

Chloroma.

This is another very rare disease and, according to Byrom Bramwell, is distinguished by the following characters:

The presence of lymphoid growths in the orbits, temporal fossæ, and periosteum of the cranial bones; the greenish colour of these growths; the studding of the bone-marrow, spleen, lymphatic glands, and viscera with lymphoid deposits; an enormous increase of the lymphocytes.

THE GRANULOMATA.

Tubercle.
Syphilis.
Leprosy.
Glanders.
Actinomycosis.

The characteristic lesion in all these diseases is the presence of a tissue resembling granulation tissue, developed round a spot at which certain specific parasitic fungi (or their toxins) have lodged.

Tubercle.

An individual or 'anatomical' tubercle may be defined as a small nodule (tuberculum) of morbid granulation tissue due to the irritative action of toxius yielded by the *B. tuberculosis*. It is non-vascular and in course of time always caseates.

The so-called 'miliary' tubercle is composed of a small cluster of such anatomical tubercles.

The tubercle bacilli, gaining access to certain regions of the body, cause there—(1) Tissue reaction, resulting in a local accumulation of cells (the tubercle), followed by (2) degeneration and necrosis (cascation).

Caseation is here described as an essential of the tubercular process, and it is assumed that the fibrosis which occurs in connection with tuberculosis is non-tubercular in nature. It is possible, however, that some of the less virulent forms of tubercle are themselves capable of organization.

In an ordinary mature anatomical tubercle three zones can be distinguished.

(*a*) The **giant-celled** or inner zone is composed of one or more large cells having processes extending outwards between the cells of the next layer. These giant cells contain large *nuclei, which are disposed at their periphery*, often in the form of a crescent. They are most abundant in slowly growing tubercles, being rarely found if the process of development is rapid. They are not distinctive of tubercle, being also present in normal granulation tissue, as well as in the morbid granulation tissue of syphilomata, leprosy and actinomycosis, and in the myeloid sarcomata.

(*b*) The **endothelioid** or middle zone consists of several layers of cells having large and distinct nuclei.

(*c*) The **lymphoid** or outer zone consists of layers of small cells identical with the lymphocytes of the blood.

No new vessels are formed in the tubercle. Those already existing become thrombosed.

If the tubercle formation be chronic, a capsule of fibrous tissue may form around it, as the result of chronic *non-tubercular* inflammation. This capsule tends to localize the process and is thus protective.

Evolution of the Tubercle.—According to the teaching of the British school of pathologists, tubercular development is as follows: The first effect of the specific toxins is to cause both the connective tissue and the endothelial cells of the invaded part to swell up and multiply. This is the origin of the so-called endothelioid cells. About the same time, or shortly after, lymphocytes from the blood immigrate to the region, and form on the outside of it a ring which constantly increases in size with the arrival of additional cells. By the continued action of the bacillary toxins, the endothelioid cells, beginning at the centre of the lesion, become still more swollen, undergo hyaline degeneration, lose their distinctness of outline, and fuse into a homogeneous mass that ultimately caseates.

If caseation does not set in too quickly, giant-cell formation may then take place.

Though the matter is still *sub judice*, the opinion is generally held that the giant cell is either a greatly enlarged endothelial cell the nucleus of which has undergone division and subdivision without the body of the cell sharing in the process; or that it is the result of the fusion of several endothelioid cells.

The bacillary toxins also poison the endothelial lining of the blood capillaries of the part; hence the thrombosis of these and the consequent non-vascularity of the tubercle.

As regards the bacilli in **human** tubercle, most of them lie *free between the cells*. Occasionally they may be noticed inside the giant-cell, in which case they may be radially arranged at its periphery.

Tubercles generally form in the lymphatics—*e.g.*, in the

case of the lungs they are found in the peri-vascular, peri-alveolar, and peri-bronchial lymphatics. Their favourite sites are the lungs, lymph glands, synovial membranes of joints, cancellous tissue of bones, pleura, peritoneum, pia mater of brain, epididymis, Fallopian tubes, and skin.

Bovine and Human Tuberculosis.—The long-debated question as to whether tuberculosis is or is not transmissible from the animal to the human being is answered emphatically in the affirmative, so far as the bovine animal is concerned, in the second interim Report of the Royal Commission on Human and Animal Tuberculosis, issued February 1, 1907.

The following are the conclusions arrived at, from which it will be seen that the Commissioners are equally emphatic in urging that the utmost care should be exercised in regard to the supply of milk:

'There can be no doubt but that in a certain number of cases the tuberculosis occurring in the human subject, especially in children, is the direct result of the introduction into the human body of the bacillus of bovine tuberculosis; and there also can be no doubt that in the majority at least of these cases the bacillus is introduced through cow's milk. Cow's milk containing bovine tubercle bacilli is clearly a cause of tuberculosis, and of fatal tuberculosis, in man.

'Of the 60 cases of human tuberculosis investigated by us, 14 of the viruses belonged to Group I.—that is to say, contained the bovine bacillus. If, instead of taking all these 60 cases, we confine ourselves to cases of tuberculosis in which the bacilli were apparently introduced into the body by way of the alimentary canal, the proportion of Group I. becomes very much larger.

'Of the total 60 cases investigated by us, 28 possessed clinical histories indicating that in them the bacillus was introduced through the alimentary canal. Of these, 13 belong to Group I. Of the 9 cases in which cervical glands were studied by us, 3, and of the 19 cases in which the lesions of abdominal tuberculosis were studied by us, 10, belong to Group I.

'These facts indicate that a very large proportion of tuberculosis contracted by ingestion is due to tubercle bacilli of bovine source.

'A very considerable amount of disease and loss of life, especially among the young, must be attributed to the consumption of cow's milk containing tubercle bacilli. The presence of tubercle bacilli in cows' milk can be detected, though with some difficulty, if the proper means be adopted, and such milk ought never to be used as food.

'There is far less difficulty in recognizing clinically that a cow is distinctly suffering from tuberculosis, in which case she may be yielding tuberculous milk. The milk coming from such a cow ought not to form part of human food, and, indeed, ought not to be used as food at all.

'Our results clearly point to the necessity of measures more stringent than those at present enforced being taken to prevent the sale or the consumption of such milk.'

These conclusions are in distinct conflict with the views held by Dr. Koch, who, in a paper read before the British Congress on Tuberculosis in London on July 23, 1901, reaffirmed his belief that the disease was not transmissible from animals to man. In fact, the Royal Commission was to all intents and purposes called into existence by that pronouncement, for it was appointed on August 31 in the same year.

The Commissioners selected were Sir Michael Foster, F.R.S., Professor Sims Woodhead (Cambridge), Professor Sidney Martin, F.R.S. (University College, London), Professor McFadyean (Principal, Royal Veterinary College), and Professor Boyce (University College, Liverpool).

Lupus.

Lupus is chronic tuberculosis of the skin (cutis vera) and mucous membranes. Typical tubercles are present, but the bacilli are few and very difficult to find. The common situation of lupus is about the nose and cheeks, but it may also occur on the trunk and limbs. When it involves the mucous membranes it generally does so by extension from the skin.

The disease rarely begins after the age of twenty-five, but it may *recur* at any age.

Syphilis.

The **chancre**, or hard sore, is the local expression of the reaction of the tissues to the *Spirochæta pallida*, and occurs at the site of inoculation. It is composed of lymphoid and endothelial cells, and occasionally of giant cells also. Necrosis soon takes place, the result being an ulcer.

The lesions of tertiary syphilis are characterized by the formation of a tissue which closely resembles ordinary granulation tissue—*i.e.*, round cells between which are **new bloodvessels**. This tissue may occur either in (*a*) concentration, when it is called a **gumma**; or (*b*) **a diffused gummatous infiltration.**

(*a*) A gumma may resolve under treatment (if begun early), or it may undergo necrosis from syphilitic endarteritis, with subsequent thrombosis of its bloodvessels.

(*b*) The gummatous material may be diffused through an organ, and may, like the gumma, resolve under treatment, if this be begun early; or it may organize into connective tissue—*e.g.*, in syphilitic cirrhosis of the liver and syphilitic orchitis.

Gummata, as Trousseau pointed out, are most liable to form on parts exposed to injury.

Leprosy.

Leprosy is characterized by the formation of granulomata arising in connection with the presence of the *Bacillus lepræ*.

The granuloma is composed principally of endothelioid cells, with occasional giant cells, and may occur either in the form of (1) distinct nodules, or (2) as a diffuse infiltration.

The tissue tends to degenerate, either being absorbed or leaving a cicatrix. There is *no caseation as in tubercle*. *Sites:* Skin, mucous membranes, nerves, testicles, liver, spleen.

Glanders.

Glanders is a highly contagious disease due to the *Bacillus mallei*, and attacking primarily horses, mules, and asses, but also communicable to man from the diseased animal.

In the horse two varieties are recognized—glanders proper and farcy—each of which may occur in the same animal at the same

time. The lesion is a granuloma, the cells of which are almost entirely composed of polymorphonuclear leucocytes, between which are the specific bacilli; no giant cells are present. In course of time necrosis takes place. Glanders proper begins (in the horse) in the septum nasi and neighbouring parts; the lymphatic glands of the neck and thorax soon become affected, and subsequently the lungs, liver, and spleen.

In the variety known as farcy the infection takes place through the skin, the disease then beginning in the superficial lymphatic vessels and glands. Secondary nodules form in internal organs, as in glanders proper.

In man the disease occurs chiefly in grooms, knackers, and those who work amongst horses, infection taking place through an abrasion of the skin or through the mucous membranes of the mouth, nose, or eyes. The symptoms may be either acute or chronic, while, as in tuberculosis, a chronic attack may at any time take on the characters of the acute form and rapidly prove fatal.

Actinomycosis.

Actinomycosis is a disease usually of cattle (oxen), occasionally of man, and is due to the growth of the actinomyces, or ray-fungus. It is probably seldom transmitted directly from one animal to another. The fungus is common on such cereals as barley, and a man may be inoculated by chewing the raw grain or by inhaling the fungus during threshing, etc.

The granuloma is at first composed principally of lymphocytes, then polymorphonuclear leucocytes appear, and giant cells are not infrequent. In the central part are clumps of the ray-fungus.

Around the granuloma the fibrous tissue is often greatly thickened, and thus the condition may be mistaken for a sarcoma. In course of time softening, suppuration, and sinus-formation occur. The pus is characteristic: it may be serous or viscid, and in either case contains the golden-yellow colonies of the parasites.

In man the common sites are the face, mouth, jaws, and neck. The infection may spread to the mediastinum. The intestines may also be attacked, and from them the disease may spread to the mesenteric glands, peritoneum, and liver. The lungs may be a primary seat of infection—as in threshers.

INFLAMMATION.

By inflammation is meant the succession of phenomena occurring in living tissues as the result of the action of an irritant—provided that irritant is not of such virulence as to kill them outright. The cause is generally a *chemical poison*, such as may be generated in the body as the result of faulty metabolism (as in gout and Bright's

disease), or bacterial activity, this latter being much the most common cause of inflammation, which is, indeed, essentially a bactericidal process. It may also result from physical agencies, such as mechanical violence, heat, electricity, Röntgen rays.

Seeing that bacteria are a potent source of inflammation, anything which diminishes the bactericidal power of the body necessarily predisposes to it. It is in this way that states of so-called lowered vitality, such as may result from privation, fatigue, chronic alcoholism, Bright's disease, promote the process.

Phenomena of Inflammation.

1. *Dilatation* of the vessels in the inflamed area (sometimes preceded by an initial constriction of the arterioles), with *acceleration* of the blood-stream.

2. *Retardation* of the blood-stream, with accumulation of the leucocytes along the walls of the bloodvessels so as to form a distinct lining (very noticeable in the small veins).

3. *Active migration* of the leucocytes into the surrounding tissues. (Some pathologists teach that the leucocytes are largely passive agents in this process.)

4. Synchronous with the escape of the leucocytes is the oozing of the lymph into the surrounding tissues in abnormal abundance.

5. Late in the process the chromocytes, which do not possess the power of independent locomotion, are squeezed through the capillary walls as the result, it is supposed, of increased intra-vascular pressure.

6. *Stagnation* of the blood-stream. The blood cells now cease to pass out.

Reaction of the Fixed Tissue Cells in Inflammation.

The fixed tissue cells of the part undergo *cloudy swelling* and *fatty* and *mucoid degeneration*. Should the inflammation be very mild and the morbid agent soon cease to act, the exudate and leucocytes are absorbed by the lymphatics, the damaged cells recover, and the part resumes its normal condition.

In more severe forms of inflammation the fixed cells of the inflamed area tend to proliferate — notably the

connective-tissue corpuscles, the vascular endothelium, and simple epithelial cells, such as those lining tubules or covering surfaces (muscle and nerve cells do not proliferate, though their nuclei may). If the inflammation persists, the derivatives of the connective-tissue cells tend to organize into fibrous tissue. Thus, all mild chronic inflammations tend to cause fibrosis of the inflamed tissue.

Suppuration.—If the inflammation is of still greater severity, as when due to the pyogenic bacteria—viz.,

Staphylococcus pyogenes aureus,
Staphylococcus pyogenes albus,
Streptococcus pyogenes,
Bacillus pyocyaneus,
Bacillus typhosus,
Bacillus coli communis,
Gonococcus,
Pneumococcus,

any of which may infect an area from the external or internal surfaces of the body or from the blood-stream (auto-infection), suppuration may occur: the phagocytes are unable to cope with the virulence of the infection: the vessels become thrombosed, the tissues are dissolved by the peptonizing action of the bacterial products, and **pus** is formed—*i.e.*, a fluid composed of exuded lymph and of the liquefied and digested tissue, holding in suspension dead leucocytes.

If the pus is pent up in the tissues, the condition is termed an **abscess**. If, on the other hand, the inflamed tissue yielding the pus abuts on a surface, the result is an **ulcer**.

The walls of the abscess cavity are formed of 'granulation tissue' (see below). The most superficial portion of this tissue is softer and more vascular than the underlying portion, from which it can be stripped off, and yielding, as it does, pus, is known as the *pyogenic membrane*. The outermost portion tends to organize into fibrous tissue, which, in a chronic abscess, may form a dense capsule, so that the abscess, if situated in such a structure as the mammary gland, *e.g.*, may feel like a solid tumour.

If we imagine a portion of the wall of an abscess cavity to be punched out, and to be embedded in some part of a

mucous membrane or the skin, we have an ulcer, which consists of a superficial pyogenic membrane and a layer of denser granulation tissue, the base and edges—in the case of an old ulcer—consisting of dense fibrous tissue.

Although in the vast majority of cases suppuration is due to the presence of pyogenic bacteria, nevertheless there are reasons for thinking that a sterile irritant may induce it in exceptional cases.

Purposes of Inflammation.—The large lymphocytes and the polymorphonuclear leucocytes possess the power of ingesting bacteria, and for this reason they have been named by Metchnikoff *phagocytes* (*phagein*, to eat). 'The phagocytes, having arrived at the spot where the intruders are found, seize them after the manner of the amœbæ, and within their bodies subject them to intracellular digestion' (Metchnikoff). The migration of the leucocytes to the inflamed area thus tends to remove *the cause* of the inflammation when of bacterial origin, and bring it to an end. The exuded lymph may serve two useful purposes —(i.) it may dilute the poison; (ii.) it may act as a bactericide. *Inflammation is not a disease, but Nature's fight against disease.*

Gangrene, Necrosis, Slough.

If the inflammation is of such virulence that there is not time for the tissues to undergo liquefaction, and they die quickly *en bloc*, while still retaining their structure, the resulting state is termed **gangrene, necrosis, or slough.**

REPAIR.

The Repair of Cells.

The essential part of the cell is the nucleus, and when a portion of the cell-body is severed, the nucleus remains, it tends to regenerate the part lost.

When a muscle fibre is cut across, the divided ends cannot unite. Such union as takes place between the ends of a divided muscle is effected by fibrous tissue.

The neurone is peculiar in regard to its power of repairing injury. When a mixed nerve is divided, the peripheral portion undergoes a series of changes; the myeline sheath and axis cylinder disappear, while the neurilemma persists, its nuclei multiplying. In the subsequent process of repair, each end plays

its part. The axis cylinder of the central end, clubbed at its extremity, elongates and travels in search of a neurilemmal sheath, often pursuing an irregular and even recurrent course in the attempt. Having found a sheath, it penetrates it, and travels along its interior to the periphery. The neurilemma now grows upwards, enveloping the naked axis cylinder, and the myeline sheath is regenerated in the whole portion of the nerve distal to the section (Mott and Sherrington).

Repair of Tissue (*e.g.*, Surgical Wounds).

When a tissue suffers a solution of continuity—*e.g.*, by the surgeon's knife or from suppurative inflammation—repair is always effected by means of *granulation tissue*, which may be defined as embryonic repair tissue. In its earlier stages it consists of small round cells, between which run newly-formed capillaries. Should the tissue have a free surface, as in the case of an open wound, abscess, or ulcer, that surface is heaped up into 'granulations,' each of which contains a loop of capillaries. Hence the term 'granulation tissue.'

The question whether inflammation is a necessary part in the process of repair of wounds is one of historical interest. Surgeons, noticing that inflammation frequently issued in repair, as in the case of septic wounds and abscesses, came to regard inflammation as a necessary antecedent to repair. When, however, with the advent of Listerism, it was found that the edges of an aseptic wound, if kept closely together, unite without any of the classical symptoms of inflammation—tumor, rubor, calor, dolor—and that the healing of wounds is satisfactory precisely in proportion as these symptoms are absent, doubt arose as to whether inflammation is in any way essential to repair, and whether the granulation-tissue formation which occurs in connection with inflammation—*e.g.*, in the tissues round an abscess cavity—does not constitute rather a separate process set on foot for the purpose of repairing the damage wrought by inflammation than part and parcel of the inflammation itself.

The whole question obviously turns upon our definition of the word 'inflammation.' The essential object of inflammation appears to be the destruction of bacteria. In the effort of destroying them the inflammatory process may, or may not, result in a solution in the continuity of the tissues. If it does not, there is no need for any reparative process and no granulation tissue need form, but if it does, a reparative process is necessary and granulation tissue is produced.

The question is whether we are to regard the changes which, in an aseptic wound healing by first intention, lead up to the formation of the repairing granulation tissue as inflammatory or not. This is largely an arbitrary question. Using the term 'inflammation' in the clinical sense, the answer should probably be in the negative.

It must not be forgotten, however, that inflammation may

lead to fibrosis, without causing any antecedent solution of continuity, as may happen, *e.g.*, in chronic inflammation of the lungs or kidneys. In such cases the fibrous formation may be of service, *e.g.*, in encapsulating a tubercular area; in others it is, so far as we can see, wholly harmful.

Granulation Tissue.—The small round cells met with in newly formed granulation tissue consist partly of leucocytes and partly of the cells descended from the fixed cells; notably those belonging to the connective tissue of the part and the endothelial lining of the bloodvessels. Under the stimulus which provokes the formation of granulation tissue, be it the cut of the surgeon's knife or a bacterial toxin leading to unmistakable inflammation, these fixed cells tend to divide. Thus, the mature tissue tends to be converted into embryonic tissue—to undergo dissolution in preparation for the process of repair, which is essentially one of evolution. The more highly endowed parenchymatous cells, such as neurones and muscle cells, take little part in forming granulation tissue. The nuclei of the neurolemma and sarcolemma may be represented in it, but neither they nor the leucocytes develop into tissue. Granulation tissue can only form one kind of tissue—*i.e.*, connective tissue—and there can be no doubt that its essential cells are derived from the local connective tissue. Its bloodvessels are formed by a proliferation of endothelial cells belonging to neighbouring vessels.

Development of Granulation Tissue.—Some of the small round cells enlarge and form endothelioid cells, and occasionally giant cells develop. It is from the endothelioid cells, or *fibroblasts*, that the permanent repair- or scar-tissue is formed.

It should be added that some regeneration of epithelial tissue may occur in the process of repair. Thus, the epithelium of the adjoining epidermis may grow over a scar, and some tubular glands appear to possess the power of regenerating their epithelial cells after they have been detached.

The Healing of Wounds.

Blood and lymph escape from the ruptured vessels. This is followed by coagulation. The chromocytes disintegrate, and their remains are carried away by the phagocytes. The now decolorized clot is replaced by granulation tissue, which consists essentially of (*a*) fibroblasts, and (*b*) newly formed blood capillaries.

(*a*) *Fibroblasts.*—These are large fusiform cells, having a single ovoid nucleus. Though probably derived from the pre-existing connective-tissue cells, by some authorities their origin is ascribed to the leucocytes and the endothelial cells lining the lymphatics and bloodvessels.

(*b*) *Newly formed Blood Capillaries.*—Coincident with the appearance of the fibroblasts, certain of the endothelial cells of the neighbouring capillaries throw out projecting buds. These elongate, become hollow, join with other similar buds from adjacent vessels, and so form loops of new capillaries.

In this manner the original blood-clot is transformed into the richly vascular *granulation tissue*. Later on, the fibroblasts enlarge and organize into fibrous tissue, the central portion persisting as a connective-tissue cell, while the outer portion is converted into fibres, though some hold that these latter are derived from a material secreted by the cell.

In course of time the newly-formed fibrous tissue contracts and obliterates most of its bloodvessels, a fact which explains the dead-white appearance of the ordinary scar.

It was once thought that primary union—*i.e.*, direct union of divided fibres and cells—took place. It is now known that, in the higher animals at least, this does not occur.

In all forms of wound-healing the process is fundamentally the same—i.e., by means of granulation tissue.

Healing by first intention is said to occur when the sides of an aseptic wound are brought into, and maintained in, apposition.

'Inflammatory lymph' is poured out, and, by coagulation, glues together the adjacent surfaces. Granulation tissue forms, and the bloodvessels from the opposite sides anastomose; organization proceeds in the ordinary way. The epithelium grows over from the edges of the wound and covers it.

Healing by second intention is said to occur when the sides of a wound have not been brought into apposition, or when sepsis has interfered with healing by first intention, or when the parts have been so damaged that suppuration or sloughing has supervened.

As in healing by first intention, inflammatory lymph is poured out and coagulates. Fibroblasts and new capillarics then appear. The new tissue projects from the base of the wound in the form of a number of small round red points, or *granulations*, each granulation consisting of loops of capillaries covered on the outside by

fibroblasts. The new tissue organizes in its deeper parts, and, *pari passu* with this, fresh granulations form on the raw surface, and in this way the wound heals up from the bottom. The epithelium grows in from the surrounding margin, and covers the cicatrix. Hair and glands are not regenerated. Contraction of the newly-formed fibrous tissue finally occurs.

In the healing of a fractured bone the process is the same as in the healing of soft tissues, with the exception that *osteoblasts* from the periosteum and endosteum take the place of, and subserve the same function as, the fibroblasts, the result being the formation of dense osseous tissue instead of dense fibrous tissue.

Diseases of Scars.

Excessive contraction, causing pain and deformities.
Keloid growth (=hypertrophy).
Ulceration.
Epithelioma.

ATROPHY.

By atrophy is meant an abnormal decrease in the size alone, or in both the size and number, of the elements of a normally developed tissue. The condition has to be distinguished from *hypoplasia*, in which there is defective development.

Atrophy is generally associated with a certain amount of fatty degeneration. It affects essentially the *parenchyma* of an organ (*e.g.*, muscle fibres, gland cells, nerve cells), the connective-tissue stroma, as a rule, escaping. The stroma, indeed, often increases in amount, a fact which has been ascribed partly to the setting free of irritating substances from the atrophying parenchyma cells, and partly to the extra blood-supply and space which their atrophy renders available for the nutrition and expansion of the remaining tissues; under the conditions of failing nutrition there is a struggle for existence among the tissue elements, the hardy connective tissues surviving and thriving at the expense of the more specialized and delicate parenchyma.

Physiological atrophy, such as occurs in the thymus, in the uterus after parturition, in the ovaries after the menopause, is known as *involution*.

The protoplasm of an atrophying cell becomes unwontedly clear, staining less than normally, and the nucleus disappears. Often there is increased pigmentation—a phenomenon well seen in brown atrophy of the senile heart.

Atrophy may be general or local.

Causes of General Atrophy.—General wasting of the tissues may be caused either by—

(*a*) *Decreased anabolism*, the result of impoverishment of the blood, such as occurs in starvation, and cancer of the œsophagus, and stomach ; or by

(*b*) *Increased katabolism*, such as occurs in severe fevers, tuberculosis, congenital syphilis. In these cases the general wasting is chiefly to be ascribed to the action of toxins in augmenting katabolism. The wasting which occurs in Graves' disease and from the administration of thyroid extract, is also due to heightened katabolism.

The Causes of Local Atrophy are—

(*a*) *Lessened Functional Activity—e.g.*, atrophy of the muscles of an arm or leg encased in splints.

(*b*) *Excessive Functional Activity.*—Usually this is preceded by hypertrophy. Examples are: the sterno-mastoids in emphysema and the biceps brachialis in file-grinders.

(*c*) *Pressure—e.g.*, atrophy of the bodies of the vertebræ or sternum owing to the pressure exerted by an aneurism ; atrophy of the liver cells caused by the pressure of the fibrous tissue in alcoholic cirrhosis.

(*d*) *Defective Neuro-trophic Influence—e.g.*, facial hemi-atrophy. We are still in the dark as to the pathology of this curious affection, but it is probably nervous in origin. The changes which take place in the muscles in consequence of disease of the lower motor neurones are rather of the nature of degeneration than atrophy.

(*e*) *Diminished Blood-Supply—e.g.*, atrophy of the testis caused by pressure on the spermatic artery by a tumour. Here, again, however, the changes are degenerative rather than simply atrophic.

Hypertrophy.

By hypertrophy is meant an abnormal increase in the *size* of the tissue elements. If the tissue elements increase in number, the term *hyperplasia* is employed. As a rule, hypertrophy and hyperplasia go hand in hand.

True hypertrophy must be distinguished from pseudo-hypertrophy. In the former there is hypertrophy principally of the parenchyma; in the latter, of the connective tissue only. Thus, in pseudo-hypertrophic paralysis some of the muscles may appear to be enormously enlarged, but the enlargement is brought about by the increase of fatty and fibrous elements, the muscle fibres themselves having largely disappeared.

The usual cause of hypertrophy is increased functional use, which is always accompanied by increased blood-supply. Familiar examples are hypertrophy of the heart in valvular disease, of one kidney when the other is removed, of one leg when the other is crippled or paralyzed. Muscular hypertrophy, if excessive, is liable to be followed by atrophy.

In some cases hypertrophy is due to the influence of an internal secretion. Substances of this kind which are capable of exciting the functional activity, or the growth, of a tissue are termed by Starling *hormones*. Secretin, which is formed during duodenal digestion, and, passing into the blood and circulating through the pancreas, excites its secretion, is an instance of the former; a substance yielded by the fœtus, which causes the mammæ to develop in the pregnant female, is an example of the latter.

Normal growth is largely controlled by hormones, which are poured out at definite periods (infancy, childhood, puberty) and determine the developmental changes incidental to these periods. If these hormones are not duly secreted, development may be arrested at any one of them, giving rise to infantilism, arrested puberty, and allied conditions. On the other hand, if they occur in excess, or are perverted, they may lead to hypertrophy: both acromegaly and gigantism are to be explained in this way.

DEGENERATIONS AND INFILTRATIONS.

The structure of the various cells of the body depends primarily upon the constitution of the zygote (=fertilized ovum) which gives origin to them. Their behaviour during life depends upon their structure as thus hereditarily determined, and upon the influences brought to bear upon them from without. These influences are *plasmic* and *non-plasmic*.

Non-Plasmic Influences.—These consist for the most part of nerve stimuli which, originating in sensory end-organs, either on the surface or in the deeper tissues of the body, are continually reverberating throughout the entire nervous system, and thus influencing not only individual neurones, but non-nervous cells attached to the ends of efferent nerve fibres. If we reflect that the human organism consists essentially of a nervous system from the ends of whose efferent nerve twigs depend so many muscle- and gland-cells, the whole being held together by connective tissue and permeated by a complex system of channels for the circulation of the body-fluids, and that nerve stimuli are ceaselessly reverberating throughout the nervous system, we shall the better realize how potently that system must influence the individual cells of the body.

Plasmic Influences.—These operate through the plasma or lymph bathing the cells and depend upon the composition of that lymph, which, again, is essentially determined by the composition of the blood plasma. This is a highly complex fluid—the most complex in nature, containing an endless variety of substances—food-stuffs, oxygen, hormones, ferments, antibodies—most of which defy the most careful and delicate methods of chemical research; and let the fact ever be remembered that it is in a fluid of this kind that, from the beginning to the end of its career, every cell in the body lies bathed, and is through it subjected to an endless variety of influences, both good and bad.

Now, the cells of the body display little or no intrinsic tendency to degeneration: *the cell environment, notably the plasmic environment, is chiefly responsible for whatever disease may affect the cell.* Even senile cell degeneration is largely extrinsic in nature, for though doubtless it is in part intrinsic—due to the running-down or wearing-out of the cell microcosm—it is even more the result of specific changes in the plasmic environment of the cell. Senility is, in fact, mainly of plasmic origin, the individual being slowly destroyed by means of his plasma—not, indeed, by any such simple and pathological process as that suggested by Metchnikoff—*i.e.*, the absorption of bacterial toxins from the large intestine—but by the operation of physiological mechanisms, the object of which is to put a definite term to the vital cycle, and thus obviate the innate tendency to immortality belonging to all living matter. In some animals—*e.g.*, the dog—these mechanisms come into operation sooner than in others—*e.g.*, man. Sometimes in man they come into premature operation, the

arteries becoming atheromatous, the skin wrinkled, and the hair grey as early, it may be, as the second decade; at others their operation is delayed, the nonogenarian being as youthful, it may be, as the average man of fifty or sixty.

If we except cases of intrinsic senile degeneration, it but very seldom happens that a cell undergoes primary degeneration. The nearest approach to such a phenomenon is afforded by the family palsies in which definite systems of neurones undergo early degeneration.

Hence, in every case of cell degeneration we should expect the existence of some morbid influence operating on the cell from without. This influence may be nervous or plasmic.

Degeneration from Nervous Causes.—A familiar instance is the degeneration which takes place in a striped muscle fibre when its motor twig is diseased. All the instances of genuine *trophic lesions* are due to some interference with the normal flow of nerve impulses into the cells 'trophically' damaged. We have still much to learn concerning this subject.

Degeneration from Plasmic Causes.—Much the most common cause of degeneration of the cell is some abnormality in respect of the plasma bathing it. Abnormalities of this kind fall under two heads:

(*a*) *Defects in the Circulation of the Plasma.*—These may be central, as in heart and lung disease; or local, as in embolism and degeneration of the peripheral bloodvessels.

Any sudden and pronounced interference with the local circulation leads to profound degenerative changes, as in infarct (see p. 43). More chronic defects of the circulation, as in chronic heart disease and senile degeneration of the arteries, lead to gradual atrophy of the parenchyma of the tissues and increase of the fibrous stroma. In the former case the sluggish circulation causes damage of the capillary walls, with escape of the chromocytes into the tissues and subsequent staining of the tissues from their disintegration, causing the well-known *brown induration* typified in the 'nutmeg liver.' In the latter case the fibrous change may be termed *senile fibrosis*, and is chiefly responsible for the toughening of the tissues observed in old age.

(*b*) *Defects in the Composition of the Plasma.*—The composition of the plasma may depart from the normal in an untold number of ways. Thus, the plasma may vary in respect of its nutrient constituents, its ferments, its hormones, and its normal waste products. Furthermore, it may be poisoned (*a*) as the result of morbid metabolism, as in diabetes; (*b*) by the introduction of a poison, such as lead or alcohol, into the body; and (*c*) by bacterial toxins formed within the body.

The vast majority of non-traumatic diseases result from the action of a morbid plasma upon the tissues bathing it. How wide is the rôle which the plasma plays in disease is evident from the fact that a toxic state of the plasma is much the most frequent cause of inflammation, and how largely this process bulks

among the diseases which the physician is called upon to treat is evident from a casual perusal of any text-book on medicine.

But morbid plasma leads to many lesions other than the inflammatory. Thus, the blood may contain substances which exert a noxious action, chiefly or entirely, upon certain kinds of cells, picking them out, as we say, by selective action, much as the pigments used for staining microscopic sections pick out some cells rather than others. A familiar instance of this is afforded by tabes dorsalis. This disease is a sequela to syphilis, and is due to the action of a poison which causes degeneration in certain sensory neurones; and it is probable that most of the 'system lesions' of the nervous system—*i.e.*, symmetrical lesions of particular tracts—have a similarly plasmic origin.

In such cases the degenerative changes are for the most part chronic. Morbid plasma may, however, set up acute destructive changes in special kinds of cells. Experiments have shown that the tissues of animals, such as the dog and the rabbit, can be made to elaborate substances capable of causing rapid destruction of special cell types, such as the chromocytes, hepatic cells, renal cells; and there can be little doubt that substances of this kind play an important part in disease. Thus, acute yellow atrophy of the liver is produced by the action of some toxin which is to all intents and purposes a hepatolysin (see p. 162), and certain forms of 'acute pancreatitis' probably own a similar pathology.

To trace out the various degenerative changes which may be produced in the tissues by morbid conditions of the plasma would be impossible, even did space permit. When we reflect that each abnormality of the plasma must tend to produce its own particular change in the tissues which that plasma bathes, it is obvious that the degenerations which protoplasm undergoes must be far more numerous than those as yet described by pathologists.

Varieties of Degeneration.

Strictly speaking, *degeneration* is simply the reverse of evolution; it is an undoing, so to speak, of evolution. Thus, when the dendrites of a neurone diminish in number, as they do in old age, or when the transverse striæ of a muscle disappear, degeneration takes place.

The pathologist, however, often uses the term 'degeneration' in the chemical rather than in the structural sense. For him it often means the conversion of the complex protoplasm into some new and much simpler substance, such as fat or colloidal material.

Degeneration must be distinguished from **infiltration**—*i.e.*, the deposition of some new substance in an otherwise unaltered cell.

Some of the more common forms of degeneration and infiltration will now be considered.

Cloudy Swelling.

In cloudy swelling the cells become swollen, their protoplasm 'cloudy' from the presence of fine granules, and the nuclei obscured. The granules are dissolved by acetic acid and alkalies, but, unlike fat, are insoluble in ether and do not stain black with osmic acid. If the degeneration has not advanced too far, the cloudiness may clear up and the cell assume its normal appearance, but if it continues to advance it may pass into fatty degeneration.

Cloudy swelling occurs in connection with febrile states. It is produced by the action of a toxin, its distribution being determined by the nature of the toxin, the organs most frequently affected being the kidney, liver, and heart.

Fatty Degeneration.

In fatty degeneration the cell protoplasm is replaced by fat. The fat first appears as minute granules, which gradually increase in number until the whole cell may be converted into a mass of fat. The fatty contents stain black with osmic acid and dissolve in alcohol and ether, but not in acetic acid.

Fatty degeneration is met with in all forms of severe anæmias—*e.g.*, pernicious, tubercular; in poisoning by certain substances—*e.g.*, phosphorus, arsenic, alcohol; and as the result of the action of bacterial toxins—*e.g.*, those of diphtheria. *Heart*, *liver*, and *kidneys* are the organs principally affected.

Fatty Infiltration.

In fatty infiltration tiny globules of fat appear in the cell, *the protoplasm of which, however, remains healthy.* The globules may coalesce and push the protoplasm against the cell wall. Fatty infiltration is the normal condition of many connective tissues (*e.g.*, of the medulla of the long bones) and, to a less extent, of the liver. *It is only when the number of fat globules exceeds the normal limit that the term 'fatty infiltration' is applicable.*

The causes are excessive diet, especially if coupled with insufficient exercise; alcoholism, particularly beer-drinking; disuse, as in the case of the muscles of a fractured limb which has been put up in splints.

Glycogenic Infiltration.

Glycogen is normally present in the liver, in embryonic tissues, and, indeed, to some extent in most cells. *As a morbid process*, infiltration of glycogen occurs in malignant tumours, and in the leucocytes in cases of suppuration, pneumonia, and other acute infections.

The test for glycogen is the mahogany-brown it gives with iodine.

Lardaceous, Amyloid, or Waxy Degeneration.

This is of the nature of an infiltration rather than a true degeneration. It is a condition in which there is an albuminous deposit in the connective tissues, particularly of *the middle and inner coats of the arterioles*. The endothelium itself is never affected, nor are parenchyma cells of any sort (muscle, gland, nerve).

The disease is met with most frequently in the liver, kidneys, and spleen. The lungs and central nervous system are exempt from it.

In 118 cases examined post-mortem by Dickinson the frequency in which the various organs were affected was as follows:

Kidney	95	Lymph glands	5
Spleen	76	Pancreas	1
Liver	65	Thyroid	1
Intestines	35	Œsophagus	1
Stomach	9	Testes	1
Suprarenals ...	9	Endocardium	1

Lardaceous material stains a deep mahogany-brown with iodine, turning blue or violet if 5 per cent. sulphuric acid is afterwards applied. With methyl violet it gives a deep rose-pink (normal tissues are stained blue).

It occurs in connection with chronic suppuration—*e.g.*,

from tubercuIosis, dysentery, and syphilis. Some say it may occur in the latter without suppuration.

In the Liver.—The organ is greatly enlarged, smooth, firm, and heavy, with its edges rounded. The cut surface is pale, translucent, and wax-like. The change *commences in the subendothelial layer of the capillaries of the intermediate zone of the liver lobule* (see Diseases of Liver), the lining endothelial cells of the capillaries remaining unaffected. The pressure of the new material upon the liver cells causes them to become fatty and to undergo atrophy.

In the Kidneys.—These organs become pale and enlarged, and the capsule strips off readily. The cut section has a translucent, bacon-like appearance. The change begins *in the vessels of the glomerular tufts and in the arteriæ rectæ*. Later on, the basement membrane of the tubules (especially of the cortex) may suffer. The lining epithelium of the tubules tends to undergo fatty degeneration, owing to interference with the circulation.

In the Spleen.—There are two varieties of lardaceous spleen :

1. The **sago-spleen**, commonest in phthisis. In this the organ is but slightly enlarged. The change begins in the arterioles and capillaries of the Malpighian bodies. On section it is seen studded with small, translucent, sago-like bodies, which vary in size from a millet-seed to a hemp-seed and give the ordinary reactions.

2. **The diffuse waxy spleen**, commonest in syphilis. The organ is greatly enlarged, and becomes hard and firm. On section it shows a uniform translucent appearance. The walls of the sinuses of the splenic pulp specially exhibit the change.

Hyaline Degeneration.

Hyaline degeneration (*hyalus*, glass) occurs in the subendothelial lining of the intima of the smaller arteries, particularly of the lymphatic glands, brain, and kidneys. The change is also to be found in tubercles prior to caseation, and in tumours. On section the material looks glassy and shining. It stains yellow with iodine.

It is of a proteid nature, and closely allied to amyloid, mucoid, and colloid material. Some authorities consider it to be but a preliminary stage of lardaceous disease.

Mucoid Degeneration.

The albuminoid *mucin* is a normal secretion of the mucous membranes, and is poured out in increased quantity when they become inflamed. It is met with as part of a degenerative process both in sarcomata and carcinomata. The affected cells and fibres swell up, and become transformed into a jelly-like substance.

In water the mucin swells up ; it is soluble in dilute alkalies, from which it is precipitated both by alcohol and acetic acid.

In ovarian cysts an allied substance—**pseudomucin**—is found. It differs from mucin in not being precipitated by acetic acid.

Colloid Degeneration.

Colloid (*kolla*, glue) is a normal constituent of the thyroid gland and the pituitary body, being derived from *epithelium*. It occurs in cystic goitre. As a degeneration, it is most frequently met with in cancers of the abdomen, especially of the stomach, intestine, ovary, and peritoneum. It also occurs in cancer of the breast, and in congenital cystic disease of the kidney.

The material resembles mucin in appearance, but is insoluble in water, and is not precipitated by alcohol nor by acetic acid.

Calcification.

Calcification is the deposition of lime salts (phosphate and carbonate) in dead or degenerated tissues.

Sites. — Arteries, especially the aorta and coronary (very rarely the veins), valves of the heart, tubercular nodules, certain tumours (*e.g.*, fibro-myomata of the uterus), the capsule enclosing the trichina spiralis, adherent pericardium, the walls of old abscesses, the fœtus of an ectopic gestation (forming lithopædion or peritoneal calculus), the thyroid, costal, and other cartilages in old people.

NECROSIS.

The term 'necrosis' (*necrōsis*, deadness) is restricted in its application to death of a portion of the bodily tissues. If it is preceded by degeneration of the cells of the affected part, it is sometimes called *necrobiosis*.

The principal forms of necrosis are: focal necrosis, fat necrosis, and coagulative necrosis.

Focal Necrosis.—In this condition numerous minute areas of tissue—generally in the *liver*, *spleen*, *kidney*, *and lymph glands*—undergo a local necrosis. The protoplasm of the part disintegrates, the cell walls disappear, and a granular substance replaces the original tissue. The necrotic foci may be either absorbed or converted into fibrous tissue.

The most probable cause is a toxin, which may act directly by killing the cells outright, or indirectly by causing capillary thrombosis. It occurs in enterica, diphtheria, and other microbic diseases.

Fat Necrosis.—This is a condition in which localized patches of necrosis are found in the fatty connective tissues of the abdomen. In a large majority of cases it is associated with pancreatic disease (*e.g.*, hæmorrhage, abscess, gangrene). It is supposed that the fat-splitting ferment (steapsin) of the pancreatic juice escapes, and acts directly upon the parts affected. It is met with typically in the *subperitoneal fat*, in which structure are to be seen, scattered throughout the normal fat, small opaque foci, ranging in size from a pin's head to a pea. The fat of the affected areas is converted into a granular material which does not stain with osmic acid.

Coagulation Necrosis.—This generally occurs in connection with inflammation, and is probably always toxic in origin. It is typically seen in diphtheria. In this disease the mucous membrane is acutely inflamed: the epithelial cells of the affected part, bathed in inflammatory lymph, are killed outright by the bacillary toxin; coagulation, both of the cell-contents and of the surrounding lymph, then takes place, and the two fuse into a homogeneous hyaline mass, which in course of time becomes grey.

Zenker's Degeneration is now regarded as a form of coagulation necrosis. It affects muscle fibres: these swell and lose their transverse striation, while the muscle-proteids coagulate into a clear homogeneous material, which soon breaks up into shiny masses of irregular shape. Zenker's degeneration is met with in continued fevers, notably enterica, and affects chiefly the abdominal muscles.

Caseation (*caseus*, cheese).—This is a variety of necrosis in which the cells disintegrate and are converted into a yellow, homogeneous, cheesy mass, composed of fatty and albuminous granules. It is most often met with in tubercular and gummatous formations and in certain rapidly-growing tumours, and is due in part to the cutting off of the blood-supply by thrombosis, and in part to toxic action.

PIGMENTATION.

'Pigmentation' (*pingo*, paint) is the term used to denote an abnormal deposit of colouring matter in the tissues. The pigment usually lies *within the cells* of the pigmented area.

Melanin.—This is the most common normal pigment of the body. It contains iron at the early stage of its formation, but later on becomes iron-free. It is bleached by chlorine, a fact which distinguishes it from carbon. It is elaborated by cell action from an albuminous substance, and is normally present in the skin, hair, iris, choroid, and cardiac muscle. The quantity of it in the skin is augmented by solar rays, at the climacteric in women, and often during pregnancy; also in leucoderma, Addison's disease, Graves' disease, granular kidney, rheumatoid arthritis. Melanin constitutes the pigment met with in melanotic sarcoma.

The **Hæmatogenous Pigments** are derived from the breaking up of the chromocytes. The principal are:

1. Iron-containing hæmosiderin.
2. Iron-free hæmatoidin.

Hæmosiderin, or *iron-containing* pigment, is found in those diseases (*e.g.*, pernicious anæmia and malaria) in which there is a pathological destruction of the chromo-

cytes. In pernicious anæmia large quantities may be found, in the form of minute granules, in the cells of the intermediate zone of the liver lobules, as well as in the spleen, renal epithelium, and bone-marrow. In the kidneys it may be present in a diffuse form.

Hæmatoidin, or *iron-free* pigment, is generally derived from extravasated blood, the hæmoglobin being first converted into hæmatin and then into hæmatoidin. It is often seen in the remains of old blood-clots in the form both of *granules* and orange-coloured rhombic *crystals*, which may remain unaltered for years.

According to Neumann, living cells are necessary for the elaboration of hæmosiderin, but not of hæmatoidin.

Pigmentation from Bile.—Jaundice is now thought to be *always* due to some form of obstruction to the outflow of bile from the liver, and to its subsequent absorption into the circulation, by which it is carried throughout the body. The pigmentation is the result of a **diffuse staining** of the tissues with bilirubin and biliverdin, and is specially marked in the conjunctiva, the skin, and beneath the tongue.

Extrinsic Pigments are those introduced into the body from without. The chief examples are—

Through the lungs	Carbon, coal, iron, or grit, deposited in the lungs and bronchial glands.
Through the alimentary tract	Arsenic, silver, deposited in the skin.
Through the skin:	Tattooing.

GANGRENE.

By **gangrene** is meant the death of the soft tissues in *mass*.

Causes.—Gangrene may result from one or more of three causes:

(*a*) Vascular obstruction—*e.g.*, embolism.

(*b*) Violent injury, destroying the tissues outright—*e.g.*, frost-bite.

(*c*) Faulty action of trophic nerves—*e.g.*, bedsores.

Etiological Classification of Gangrene.

- (*a*) From vascular obstruction
  - Arterial
    - Embolism, thrombosis.
    - Degeneration: Endarteritis obliterans; senile degeneration.
    - Spasm: Ergotism, Raynaud's disease.
  - Venous
    - Thrombosis.
    - Bandage, splint-pressure.
    - Pressure in acute inflammation.
    - Strangulated hernia.
  - Capillary
    - Thrombosis from bacterial toxins, causing septic gangrene
      - Carbuncle.
      - Sloughing phagedena.
      - Cancrum oris.
      - Acute spreading traumatic (=malignant) œdema.
- (*b*) From destruction of the tissues outright
  - Frost-bite.
  - Burns.
  - Corrosive poisons. (Possibly septic gangrene may partly be due to the destructive action of the toxins on the living protoplasm.)
- (*c*) From faulty action of trophic nerves
  - Bedsores, after spinal injury.

Clinically there are two main varieties of gangrene—the dry and the moist. The former only occurs when the arterial afflux is interfered with, and it is most apt to result from gradual arterial obliteration, as in senile gangrene. In other cases, as from arrest of the venous efflux or sepsis, the gangrene is moist.

Dry Gangrene is met with typically as senile gangrene. The arteries of the leg, narrowed and rigid from calcareous degeneration, become gradually thrombosed, and the blood-supply being thus cut off, gangrene results. The part becomes purple or mottled, owing to extravasation of hæmoglobin from the vessels. In consequence of the evaporation which takes place from the surface, the tissues shrink and wither, and the skin assumes the appearance of parchment, ultimately becoming covered with an oily film from transudation of the underlying fat.

If the process is arrested, the dead part acts as an irritant to the adjacent living tissues, with the result that a dusky-red zone of inflammation forms, called *the line of demarcation*. Finally, the dead part is separated from the living by suppuration.

Constitutional infection is rare in dry gangrene, the dried up, shrunken tissues not constituting a suitable soil for the growth of organisms.

Moist Gangrene is usually the result of a severe inflammation arising from microbic infection. The vessels are thrombosed as the result of toxic action, and the gangrenous part becomes soaked in an albuminous fluid containing many disintegrated chromocytes. The dissolved-out hæmoglobin, diffusing itself through the fluids, stains the dead tissues. Later on, *bullæ*, containing a blood-tinged fluid, form. Still later, gases are generated from infection by the *Bacillus aërogenes capsulatus* of Welch, giving rise to emphysematous crackling. Ultimately the part putrefies, and constitutional infection occurs.

Diabetic Gangrene would appear to be the outcome of four conditions: (1) Lowered vitality, (2) endarteritis, (3) peripheral neuritis, (4) the presence of sugar, which is a good culture medium for bacteria.

ŒDEMA AND DROPSY—THROMBOSIS—EMBOLISM.

Œdema and Dropsy.

All the tissues are bathed in a fluid—lymph—which is a very dilute kind of blood-plasma (see table). The lymph is continually oozing through the thin capillary walls and diffusing itself slowly among the tissues, to which it supplies the various substances needful to their vitality; it collects the waste products of metabolism, and ultimately flows into the venous system by the thoracic ducts.

Though the question is not yet settled, we may provisionally assume that the separation of the lymph from the blood is in part—

Physical { Filtration. Osmosis. Dialysis.

and in part—

Vital { The endothelial cells of the capillary walls actively secrete the lymph from the plasma.

An undue accumulation of lymph in any part of the body is known as dropsy. When the fluid accumulates between the individual cells of a tissue, causing it to swell and become puffy, the condition is termed 'œdema.'

Œdema of the subcutaneous tissues is known as **anasarca**; dropsy of the lateral ventricles of the brain as **hydrocephalus**; of the peritoneum as **ascites**; of the pleura as **hydrothorax**; of the pericardium as **hydropericardium**; and of the tunica vaginalis as **hydrocele**.

The degree of œdema is determined by the looseness or denseness of the tissue affected—*e.g.*, the subcutaneous tissues and lungs are capable of great distension, whereas the solid organs, possessing dense capsules, such as the kidneys and testis, can swell but little.

Dropsical fluids are much richer than normal lymph in proteids (see table).

The following table from Halliburton shows the composition of dropsical fluids as compared with the normal fluids of the body:

Fluid.	Parts per 1,000.			
	Solids.	Water.	Proteids.	Salts.
Blood-plasma	97·10	902·90	82·89	8·55
Normal lymph	13·66	986·34	3·37	8·78
Pleuritic fluid	36·05	963·95	28·50	7·55
Ascitic fluid	39·51	960·49	29·73	5·94
Hydrocele fluid	61·15	938·85	50·05	9·26

Theories to explain Dropsy.—Dropsy was originally thought to be due to an abnormally watery condition of the blood, but that this *per se* is incompetent to cause it is proved by the fact that the injection of large quantities of salt solution is not followed by it.

The chief causes of dropsy may be classed as—(i.) *mechanical*, (ii.) *toxic*.

(i.) *Mechanical.*—Examples of this are : tight bandages applied to arm or leg, pressure of enlarged glands in axilla ; failing compensation in heart disease; obstruction to the portal circulation in the liver (cirrhosis, cancer), causing ascites.

(ii.) *Toxic.*—This cause operates in such diseases as nephritis and beri-beri. It is supposed that the toxin effects some *damage to the endothelium of the capillary walls, whereby they become more permeable to fluids*, certain capillaries, such as those of the face, being more susceptible to this influence than others. Hence the early occurrence of œdema of the face in Bright's disease (see chapter on Kidneys).

Acute Circumscribed Œdema (Angio-neurotic) is characterized by the sudden appearance at times of transient, sharply-defined, tense and shiny œdematous swellings on the eyelids and other parts of the face, hands, genitals, etc. It was first described in 1880 by Quincke, and would appear to be due to some form of alimentary toxæmia.

Thrombosis.

Thrombosis (*thrombos*, a clot) means the coagulation of blood, *during life*, in any part of the cardio-vascular system—heart, arteries, capillaries, or veins.

The essential primary change in the formation of a thrombus appears to be the accumulation and fusion of blood-plates into a mass, and their adhesion to a damaged part. According to Greenfield, the leucocytes under ordinary conditions take no active part in thrombus formation.

Causes.—(*a*) Changes in the vessel walls; (*b*) changes in the composition of the blood; (*c*) retardation of the blood-flow.

Frequently two or all of these causes co-operate.

(*a*) **Changes in the Vessel Walls.**—Damage to the endothelial lining of the vessel walls is the most important factor here. Atheroma, primary calcification, etc., do not cause thrombosis, *unless the endothelial lining is injured or destroyed.*

(*b*) **Changes in the Blood.**—These are such as cause *increased coagulability.* As Wright has shown, throm-

bosis of the femoral vein in enteric fever is usually preceded by increased power of coagulation, the result, he assumes, of the excess of calcium salts furnished by the milk diet.

Certain poisons may also operate *by increasing the fibrin-ferment—e.g.*, toxins, protooses, snake-venom. In enteric fever there probably also occurs a subendothelial infiltration (of toxic origin), which impairs the vitality of the endothelium itself.

Agglutination of the chromocytes, as in enterica and pneumonia, may also predispose to thrombosis.

(*c*) **Changes in the Blood-Flow.**—Retardation, or even arrest, of the blood-flow is by itself incompetent to cause thrombosis, for it has been proved that if a bloodvessel is ligatured in two places under strict antiseptic precautions, and care is taken not to injure the endothelial lining, the stagnant blood may remain fluid for weeks or months. Nevertheless, it is an important contributory factor in thrombosis. Witness the effect of compressing or ligaturing the artery in aneurism, and the tendency to thrombosis of the venous sinuses within the skull when the circulation is languid, as in the aged and moribund.

Thrombosis occurs most frequently in the *veins.* Venous thrombosis is fifty times more common in the leg than in the arm.

Septicæmia, pyæmia, and other infective diseases, would appear to cause thrombosis in part by increasing the coagulability of the blood, and in part by damaging the endothelial lining of the bloodvessels.

Appearance of a Thrombus.—If it forms slowly, it is of greyish-white colour and laminated (=active clot); if it forms quickly, it is red and non-laminated (=passive clot). Intermediate forms may occur.

Post-mortem clots differ from thrombi in being softer, never laminated, and non-adherent to the vessel walls.

Fate of Thrombi.

Absorption.
Organization.
Calcification (phleboliths).
Disintegration, causing aseptic emboli.
Septic infection, which always results in disintegration (*e.g.*, by suppuration) and the formation of septic emboli.

Embolism.

Embolism signifies the lodgment of some solid substance in a vessel too small to allow it to pass on. The impacting body is carried into position by the circulation, and is called an *embolus*. Emboli occur chiefly in the arteries as these diminish in size in the direction of the circulation; also in the portal vein, which divides like an artery. They are most frequent in the renal, splenic, and cerebral arteries.

An embolus of a systemic artery is derived from the left heart or systemic arteries; an embolus of the pulmonary artery is derived from the right heart, or systemic veins. A very small embolus may pass through the pulmonary capillaries into the general circulation.

Varieties—

Embolism from a detached portion of a thrombus.

Embolism from a portion of an inflamed or degenerated heart-valve.

Embolism from detachment of an atheromatous patch in an artery.

Embolism from detachment of a portion of a tumour (*e.g.*, sarcoma).

Embolism consisting of masses of vegetable parasites (*e.g.*, *Bacillus anthracis*).

Embolism consisting of animal parasites (*e.g.*, those of malaria).

Fat emboli.

Air emboli.

Effects of Embolism.—If there is *free collateral circulation*, as in the case of the muscles, skin, and bone, secondary thrombosis takes place on each side of the plug, and extends up and down the blocked vessel as far as the nearest branches. The clot then organizes, and a small portion of the artery becomes obliterated, but the tissues do not suffer in nutrition because the collateral vessels carry on the circulation.

If a large and important vessel, such as the pulmonary or coronary artery, is blocked, sudden death may result.

Infarcts.

'End' or 'Terminal' Artery.—By this is meant an artery which, though it has capillary, *has no arterial, anastomosis with neighbouring vessels.* Such arteries exist in the spleen, kidneys, intestines, brain (base), spinal cord (grey matter), retina, heart, and coronary arteries. The peripheral branches of the pulmonary and superior mesenteric arteries are also to some extent end-arteries. An end-artery generally supplies a cone-shaped area of tissue, the base of the cone being on the surface of the organ.

An **infarct** (*farcio*, 'I stuff') is a degenerated mass of tissue supplied by an end-artery which has been blocked by an embolus. At the moment of occlusion the blood is driven into the companion vein by reason of the contraction of the part of the artery lying distal to the plug, and local anæmia results. The affected area of tissue is usually cone-shaped, the base of the cone being at the surface of the organ (from which, if recent, it may project slightly), and the apex at the point of obstruction.

The infarct may be either *red* or *white*. This difference in appearance depends upon *the vascular peculiarities of the organ in which it occurs.* If the area is totally and permanently deprived of blood, the infarct is *white* or *anæmic;* while if a certain amount of blood can enter from neighbouring arterioles and capillaries, the infarct is *red* or hæmorrhagic.

Red infarcts are found most typically in the lungs, medulla of kidney, and spleen. Their colour is the *result of hæmorrhage into the substance of the infarct.* Cohnheim's theory that it is due to reflux from the veins is now abandoned by pathologists. In course of time the infarct becomes encapsuled with fibrous tissue, the colouring matter absorbed, and the affected area converted into a scar.

In the white or anæmic infarct *hæmorrhage is absent.* It occurs typically in the cortex of the kidney and the spleen, brain (except the cortex), spinal cord, and heart. In the case of the kidneys the result of suddenly cutting off the blood-supply is to cause coagulation-necrosis of the cells lining the tubules.

Embolism of an end-artery in the brain gives rise to necrosis of the blocked area, followed by softening and liquefaction.

Infarct of the liver does not occur, because the portal vein, though like an end-artery in its distribution, connects freely with the hepatic artery through the medium of the capillaries.

Fat Emboli are composed of globules of liquid fat. They are most frequently met with in the arterioles and capillaries of the lungs, and generally occur in connection with injuries of the long bones, especially of those near the epiphyses, the veins in the cancellous tissue of which, being large and patent, allow the liberated marrow cells to enter the circulation and thereby reach the lungs. Some of the smaller particles may pass through the lungs and lodge in the brain, heart, or kidneys.

Air Embolism. — This condition may result from wounds about the root of the neck (the 'dangerous area'). The blood-pressure in the large veins entering the thorax being negative, air is sucked into the right heart, and the branches of the pulmonary artery are found full of frothy blood.

It is probable that most of the alleged cases of air embolism are the work of gas-producing bacteria.

DISEASES OF THE KIDNEYS.

Chief Constituents of Normal Urine.

	Men.	Women.
Total in twenty-four hours ...	1,400-1,600 c.c.	1,200-1,440 c.c.
Total of urea	35 grammes.	30 grammes.
Percentage of urea	2·35 per cent.	2·3 per cent.
Total of uric acid (Hopkins)	1 gramme.	0·857 gramme.
Percentage of uric acid ...	0·066 per cent.	0·066 per cent.
Ratio of uric acid to urea...	1 to 35.	1 to 35.
Total of chlorine (Parkes) ...	7·5 grammes.	6·75 grammes.
Percentage of chlorine ...	0·5 per cent.	0·52 per cent.
Expressed as NaCl	0·825 per cent.	0·858 per cent.
Total of P_2O_5	3·16 grammes.	2·8 grammes.
Percentage of P_2O_5	0·21 per cent.	0·22 per cent.

The normal kidney is about 4 inches long, 2½ inches broad, 1½ inches thick, and its weight is about 4½ ounces.

The main function of the kidneys is the excretion of the nitrogenous waste products of the tissues—urea, uric acid, etc. (The kidneys also eliminate sulphates, chlorides, phosphates, etc.; these salts do not represent tissue metabolism, but are simply

those contained in the food swallowed.) The urea, uric acid, etc., are not manufactured in the kidney from raw material, but pre-exist as such in the blood, and are removed from it by the renal epithelium (chiefly of the convoluted tubules) by a vital process of excretion. The salts and water are passed through the glomeruli by a biophysical process of filtration.

Urotoxins.—According to Bouchard, a number of toxins are present in healthy urine. If 60 c.c. of normal urine be injected into the veins of a rabbit, the animal dies.

The existence of *an internal secretion* has not been satisfactorily proved, nor has that of secretory nerves, but the kidneys are abundantly supplied with *vaso-motor nerves.*

FIG. 3.—CORTEX OF KIDNEY.

1, Interlobular artery; 2, Malpighian body; 3, convoluted tubule.

Dr. Richard Bright in 1827 drew attention to the fact that dropsy and albuminuria are often associated with disease of the kidneys.

Although the term 'Bright's disease' is clinical rather than pathological, it is convenient to use it as synonymous with 'nephritis.'

It is probable that all forms of nephritis are caused by the action of poisons brought by the blood-stream to the kidneys and damaging the renal substance.

These poisons may be absorbed from the oro-alimentary tube, or be derived from bacteria in the blood and lymph, or they may be products of a faulty metabolism of the tissues. On this hypothesis, quickly-acting poisons cause acute nephritis; slowly-acting poisons, chronic nephritis.

We must suppose that these poisons are especially destructive to the renal epithelium. Possibly the great excretory capacity of the kidneys may lead to an accumulation of such poisons in the renal substance.

There can be little doubt, for example, that scarlatinal nephritis is due to a bacteriogenetic toxin. Vast quantities of the specific toxin are manufactured, and being eliminated largely by the

kidneys, in certain cases the renal substance may be so irritated during the process of excretion that scarlatinal nephritis is set up.

In Bright's disease all the constituent parts of the kidney are involved to a greater or less extent—viz., the glomeruli, the renal epithelium, and the intertubular tissue, although in the different kinds of nephritis these structures are affected in different degrees.

In both acute and chronic nephritis the most conspicuous pathological changes are to be seen in the cortex of the kidney, especially in those parts of it where physiological activity is greatest—that is, in the *glomeruli* and *convoluted tubules*.

Acute Nephritis (Parenchymatous, Desquamative).

There are two classical forms of acute nephritis, each varying with the nature of the particular toxin that causes it. In the one form the stress of the inflammation falls more especially upon the tubular epithelium—*tubular nephritis*—and in the other upon the glomeruli—*glomerular nephritis*.

The kidneys become congested and swollen. The glomerular vessels may rupture, causing blood to appear in the urine. The lining epithelial cells swell up, proliferate, and become detached, in some cases choking the tubules.

Exudation of inflammatory lymph takes place in the direction of least resistance—*i.e.*, *into the tubules*, which, swelling up and thus being pressed against one another, prevent the exudation of much lymph between them. The intra-tubular lymph coagulates, and so forms a mould or *cast* of the tubule. The detached epithelial cells may adhere to the outside of the cast, producing an *epithelial cast*. Later on, the shed epithelium may undergo various kinds of degeneration, the result being the formation of *granular*, *fatty*, and other casts. If the cast consists of a plain mould of the interior of the tubule without any cell elements, it is known as a *hyaline* cast.

The damaged tubules allow the escape into the urine of serum albumin and serum globulin (but never fibrinogen). The casts and shed epithelium tend to block some of the tubules, and this in part explains the scanty urine of acute nephritis.

When recovery sets in, the inflammatory products are in part expelled into the urine and in part absorbed. Some of the tubules are rendered *hors de combat* and atrophy, whilst others, hitherto imperfectly developed, attain full physiological maturity and compensate in function for those irreparably damaged.

The Large White Kidney.—If recovery does not ensue and the disease becomes chronic, we have the condition known as 'large white kidney.'

The organ is now enlarged (the two together may weigh 28 ounces, as against 9 ounces in health), and the capsule readily strips off, leaving a smooth surface. On section the cortex is seen to be thickened, pale, and mottled. The convoluted tubules are filled with detached epithelial cells in a state of fatty and granular degeneration, fatty and granular casts occupy the straight tubules, and there is a proliferation of the epithelium within the capsule of Bowman. Small embryonic cells, which may later develop into tissue fibres, make their appearance between the tubules.

The patient generally dies at this stage, either from uræmia or some visceral inflammation (pericarditis, pneumonia, pleurisy). If he continues to live, the disease passes into the stage of secondary chronic interstitial nephritis, allied to granular kidney. Some hold that it may pass into

The Pale Granular Kidney.—In this the cortex may be of normal thickness or much reduced in size, according to the time the disease has lasted. In a typical case the organ is pale, fibrous, shrunken, and granular on the surface. Detached epithelial cells are seen in the tubules. Many of the tubules and glomerular tufts are atrophied.

It is probable, as Dr. Rose Bradford contends, that the pale granular kidney is a chronic disease from the beginning, and not a development from a preceding acute stage.

Red Granular Contracted Kidney (Primary Chronic Interstitial Nephritis, Gouty Kidney, etc.).—Red granular contracted kidney is probably not a sequel to acute nephritis, but a chronic disease *ab initio*, due to the long-continued action of a renal poison. It is of frequent occurrence after the age of forty, and very insidious in its course, sometimes not being diagnosed until near its

fatal termination. The kidneys are small, sometimes remarkably so, Hilton Fagge quoting a case in which the two together weighed under 1½ ounces. The capsule is thickened and adherent, and, when removed, portions of kidney tissue are pulled off with it, the exposed surface showing small granulations, varying in size from $\frac{1}{16}$ to $\frac{1}{8}$ inch. The colour is usually a dark red. On section the cortex is seen to be shrunken, often being reduced to a mere shell of but $\frac{1}{4}$ to $\frac{1}{8}$ inch in thickness, and here and there small cysts are present.

The disease may occur secondarily to the long-continued action of such a poison as lead, or in association with gout; but it often occurs as a primary disease in those leading perfectly healthy lives, in which case it probably arises from the action of a renal poison generated as the result of some metabolic vice.

The pathological changes are essentially—

(*a*) *A fibrosis*, with
(*b*) *Tubular and glomerular degeneration.*

Some hold that the fibrosis constitutes the primary change, the parenchymatous atrophy being secondary to this.

The fibrosis has the following distribution :

(i.) *Peri-arterial.*
(ii.) *Peri-glomerular.*
(iii.) *Peri-tubular.*

(i.) The peri-arterial fibrosis occurs especially in connection with the interlobular arteries. The strands of fibrous tissue around these vessels contract, and this explains the depressions between the granulations on the surface of the organ.

The intra-renal arteries are also themselves considerably thickened, notably their inner coats. The media shows a tendency to atrophy (Russell).

(ii.) The capsule of Bowman is greatly thickened, and the entire glomerulus may be converted into a laminated fibrous ball.

(iii.) The pressure of the fibrous tissue between the tubules, coupled with the atrophy of the glomerular capillaries as explained in (ii.), leads to considerable atrophy of the tubules, though it is possible that the

atrophy of the renal epithelium is largely primary, and due to the action of a renal poison.

The cysts in the cortex are due to the distension of tubules, the channels of which have been constricted by the new tissue.

Correlative Pathological Changes in Chronic Nephritis.—When once Bright's disease has become chronic, there occur, with rare exceptions, *cardio-vascular changes.* The left ventricle of the heart becomes hypertrophied, the smaller arteries are thickened by increase in their muscular and fibrous tissue, and atheroma is often present in the larger arteries and in those at the base of the brain.

These changes are most characteristically seen in granular kidney. Their pathology has excited much controversy, and no two authorities appear to agree on the subject. It is, perhaps, somewhat as follows:

Early in the disease a substance having a vaso-constrictor action circulates in the blood. What this substance is, or whether it is the one which is responsible for the progressive renal disorganization which characterizes this disease, it is impossible to say, but it is probably not the result of defective renal excretion, as its effects are observed long before the kidneys are seriously disorganized.

The substance in question causes a widespread constriction (hypertonus) of the systemic arterioles, the intra-renal arterioles remaining relaxed. Now these are the vaso-motor conditions most favourable for diuresis—*i.e.*, an increased pressure in the systemic arteries, including the renal, and a diminution in the resistance offered by the intra-renal arterioles, leading to a great augmentation in the pressure, and a corresponding increased rate of blood-flow, within the renal capillaries. In short, the vaso-constrictor substance, which is ever present, brings about just those vaso-motor conditions which are most favourable to its elimination.

The constriction involves the arterioles essentially; it is here that the augmented vascular resistance of Bright's disease resides; the view that it is situated in the capillaries is untenable. The hypertonus tends, however, to involve the entire systemic arterial tree, the pre-arteriolar constriction being probably of a compensatory nature,

tending, as it does, to protect the arteries from the stretching effect of the heightened blood-pressure. Thus, the radial arteries in granular kidney often feel small, 'tightened up,' and incompressible. These may, however, be large and incompressible, and in such cases the hypertonus, in the upper extremities at least, is limited to the arterioles.

This condition of arterial hypertonus leads to hypertrophy of the media of the hypertonic arteries, and to hypertrophy of the left ventricle, which, owing to the augmented peripheral resistance, has increased work put upon it. On the other hand, the media of the hypotonic intra-renal arteries tends to atrophy.

In the hypertonic arteries the intima and adventitia stand in sharp contrast as regards the influences they are subjected to, for while a hypertonic media protects the enveloping adventitia from the augmented blood-pressure, the intima receives the full brunt of that pressure, as does also the endocardium of the left ventricle; and this state of things continuing hour by hour, by day and by night, year after year, it is not surprising that both these structures should undergo some responsive change. Briefly, they tend to thicken, while the large arteries and the left ventricle, especially in the region of the valves, become atheromatous.

A further effect of the augmented blood-pressure is that the left ventricle and entire systemic arterial tree tend to dilate, the extent to which they do so depending upon the behaviour of their muscular elements.

So long as the muscular tissue of the heart remains sound it is capable of effectual systole, but when that tissue degenerates, as in process of time it does, the degenerated muscular fibres being replaced by fibrous tissue, the left ventricle fails to empty itself adequately during systole, an excess of residual blood remains after systole, and thus by degrees it comes about that the left ventricle, over-distended during its stretchable phase of diastolic relaxation by this load of residual blood, together with that flowing in from the lungs, becomes unduly stretched, and yields—*i.e.*, *dilates*.

Similarly, the extent to which the arteries become stretched, giving rise to tortuosity and dilatation, depends

upon the condition of the muscular media. If we suppose hypertonus to be maintained fairly generally throughout the arterial tree, it is probable that in the hypertonic region little or no stretching will occur until the muscular elements have been to a large extent replaced, as they tend to be, by a hyaline fibroid material. In those arteries, however, which do not become hypertonic, early stretching is likely to occur. Thus, in the cases in which the radial arteries are tightly contracted, these vessels may long remain quite straight and undilated—even, indeed, throughout the entire course of the disease; but in those cases in which the radials tend towards a state of hypotonus, they early become dilated and tortuous. It is probable also that the occurrence or absence of a dilated aorta in granular kidney largely depends upon the degree of tonicity of the vessel.

The adventitia tends to remain unaffected in granular kidney, so long as it is protected by a hypertonic media. If the media does not become hypertonic, or if, in process of time, a hypertonic media degenerates, the adventitia yields before the augmented blood-preasure and undergoes compensatory thickening.

Among the other results of the heightened blood-pressure in granular kidney are the formation of miliary aneurisius in the cerebral arteries.

In chronic Bright's disease, and especially in granular contracted kidney, there is a marked tendency to *hæmorrhage*. As Hale White puts it: '*A fact which you cannot too importantly remember is that a person with Bright's disease may bleed from anywhere—e.g.*, from the brain, retina, lobe of the ear, nose, lungs, alimentary and urinary tracts.'

Patients with granular kidney generally have emphysematous lungs.

Pleurisy, pericarditis, and pneumonia are common complications of Bright's disease, whether acute or chronic.

Albuminuric retinitis is met with only in chronic forms of renal disease, and occurs in about 28 per cent. of the cases. The prognosis is very unfavourable, most of the patients dying within a few months after the retinal changes are first observed.

Scarlatinal Nephritis.

In this form of Bright's disease the general phenomena are the same as described under acute nephritis, but there are some special points to be mentioned in connection with it. The scarlatinal poison specially picks out the Malpighian bodies and the small arteries connected therewith. The intima of these arterioles, particularly that of the afferent vessels of the glomeruli, undergoes hyaline degeneration. Bowman's capsule is swollen, and the cells of its epithelial lining proliferate, in some cases to such a marked extent as almost to fill up its interior and, by compressing the glomerular tuft, to cause its atrophy.

Should the disease become chronic (one to three years' time), the whole Malpighian body may be seen to be composed of concentric laminæ of fibrous tissue, with complete obliteration of the glomerular tufts. The branches of the renal artery become thickened from chronic endarteritis and peri-arteritis.

Transitory Nephritis.

In the albuminuria of pneumonia, enterica, diphtheria, and other febrile disorders, a toxin must in some way damage the tubules, allowing the escape of the albuminous constituents of the blood. When this happens, the condition is known as transitory nephritis.

The ingestion of turpentine, cantharides, mercury, and other poisons, may also cause albuminuria. Cantharides in some cases induces a marked glomerular nephritis, in many respects resembling scarlatinal nephritis.

In *secondary syphilis* there may be albuminuria, due, probably, to an injury inflicted on the renal epithelium by the specific toxin.

In *tertiary syphilis* there may be either a diffuse gummatous infiltration of the kidney or the development in it of definite gummata (as in the case of the liver).

The urine in these syphilitic cases may contain abundant albumin, yet dropsy and the other symptoms of Bright's disease may be absent.

Tuberculosis of the Kidneys.

Tuberculosis of the kidneys may be met with in three forms—

(i.) As an extension from the epididymis by way of the vas deferens, vesiculæ seminales, trigone of the bladder, and ureter.

(ii.) As part and parcel of a general tuberculosis.
(iii.) As primary tuberculosis of the kidney.

Congenital Cystic Disease.

In this condition the kidneys are greatly enlarged and converted into a mass of cysts, suggesting in appearance a bunch of grapes. The proper kidney substance is atrophied. The disease is usually considered to be due to some anomaly in development, or else to an inflammation of the papillæ—causing occlusion of the ducts.

A similar general cystic disease of the kidneys is sometimes, but very rarely, met with in adults. In this form also the kidneys are greatly enlarged, and may weigh from 1 to 6 pounds. The cysts, separated by the remains of the renal tissue, are lined with epithelium and contain an albuminous fluid.

Hydronephrosis.

Hydronephrosis is the condition in which the kidney is converted, partially or entirely, into a cyst, as the result of some obstruction to the urinary outflow. The pelvis and the calices are first dilated, then the medulla becomes atrophied, the process of atrophy starting at the papillæ and spreading outwards, and ultimately the kidney is transformed into a mere cyst, which may be either small or of considerable size. The condition may be congenital or acquired, and unilateral or bilateral, according as the obstruction affects one or both sides.

The congenital causes are developmental abnormalities of the ureter and imperforate urethra; the causes in later life are such conditions as the presence of a calculus in the ureter, cicatricial contraction of the ureter, pressure on the ureter by a growth (*e.g.*, carcinoma of the uterus), enlarged prostate, and stricture of the urethra.

Tumours of the Kidney.

These are rare. A peculiar form of sarcoma, called *rhabdosarcoma*, owing to the admixture of striated muscle fibres, is sometimes found in infants. (It is noteworthy in this connection that the kidneys and the muscles are alike developed from the mesoblast.) Other tumours of the kidneys are adenoma, sarcoma, and carcinoma. Sarcoma is the most frequent malignant tumour, and generally occurs in children.

DISEASES OF THE LUNGS.

The lungs are developed as outgrowths of the œsophagus. The epithelium lining the air-cells, bronchi, and trachea is derived from the hypoblast, and the rest of the lung-tissue from the mesoblast.

Collapse of the Lung.

Atelectasis is the condition of the lungs in the stillborn. They are completely airless, and sink in water.

The causes of collapse of the lungs are :

(i.) Pressure from without { air, serum, pus, blood, aneurism, tumours.

(ii.) Obstruction from within, caused by blockage of bronchi.

The chief condition which leads to obstruction of the bronchi is 'capillary bronchitis,' in which the small tubes become plugged with viscid mucus. The imprisoned air is absorbed by the blood, and the alveolar walls, falling together, ultimately lie in contact.

Collapsed lung is reduced in size, of a dark red colour, and non-crepitant; it sinks in water.

Emphysema.

There are two main varieties of emphysema—the *true* and the *spurious*.

In *spurious* emphysema (insufflation) the lungs may remain unduly expanded for some days, but there is no rupture of the air vesicles. It occurs chiefly in children, as the result of capillary bronchitis and catarrhal pneumonia.

In *true* emphysema an actual rupture of the pulmonary air vesicles occurs. There are two kinds : the *interlobular*, in which the air escapes into the interlobular spaces, and may thus gain access to the mediastinum and thence to the subcutaneous tissue of the neck and chest; and the *vesicular*, in which adjacent vesicles run into one another.

Vesicular Emphysema.—This is the variety that is generally meant by pulmonary emphysema. It may occur in a localized or generalized form. In the former it is met with in the neighbourhood of pleuritic adhesions, or in parts of the lungs which have been placed out of action—*e.g.*, by tubercle or collapse. In these localized

Expiratory = Substantival Emphysema
Inspiratory - Complementary or Vicarious Emphysema

forms the essential cause is undue traction on the vesicular walls, in consequence of which their nutrition fails and rupture occurs.

In generalized vesicular emphysema a degeneration of the vesicles takes place throughout the entire lungs; their bloodvessels and endothelian lining atrophy, they lose their elasticity, and the septa between adjacent vesicles give way. At the same time the vesicular walls lose their wavy outline, presenting under the microscope a stretched appearance.

This variety of emphysema is essentially due to *primary atrophic degeneration*. Such degeneration takes place in every one with advancing years, but in some it is met with in early adult life or even before this. It is especially apt to occur in connection with certain diseases, such as gout and granular kidney.

The second, but much less important, factor in the production of this form of emphysema is *long continued over-stretching of the vesicular walls*. Such over-stretching may result from (*a*) excessive pressure from within, as happens when a powerful expiration is made while egress to the air is impeded, as by a completely or partially closed glottis (muscular effort, coughing), or in blowing wind instruments; or it may result from (*b*) excessive traction from without. We have seen that the latter is the chief factor in determining localized emphysema. It may also be a minor factor in causing generalized emphysema: in all forms of breathlessness other than those due to obstruction in the respiratory passages (as by the diphtheritic membrane or by throttling), the mean size of the chest is increased by the preponderating action of the inspiratory muscles (the expiratory muscles remaining in partial or complete abeyance). This is because the inspiratory position of the chest is the one most favourable to the pulmonary circulation (Campbell). Hence it is probable that whatever promotes breathlessness may predispose to emphysema, whether it be physiological breathlessness, such as results from athletic pursuits, or pathological breathlessness, such as occurs in asthma and heart disease.

In generalized emphysema the lungs may be unduly expanded (hypertrophous emphysema), or not more than

their average size (atrophous emphysema). In the latter case it is probable that the disease has not occurred until the thoracic cage has undergone senile fixation. When it occurs before this the mean size of the chest (owing to the favouring influence of the inspiratory position on pulmonary circulation) undergoes steady increase from over-action of the inspiratory muscles (Campbell). As a result, these latter shorten (as happens in the case of talipes), and so fix the chest in the inspiratory position. In this way the chest, in the later stages of the disease, may be fixed in a position of super-extraordinary inspiration—*i.e.*, the patient is unable, by the most powerful expiratory effort, to reduce his thorax to normal dimensions.

It will generally be found that the chest expands as middle life is reached, especially in stout people. Men are apt to pride themselves then on possessing a 40-inch chest, ignorant of the fact that it generally indicates degeneration. It takes place in obedience to the principle already enunciated, and is in large measure due to loss of pulmonary elasticity; in order to maintain physiological conditions it is necessary that the pulmonary tissue shall be kept in a certain degree of tautness (otherwise 'pulmonary suction' lessens), and as the pulmonary fibres lengthen they need to be tightened up—tuned up to the normal pitch, so to speak—by an increase in the mean size of the chest.

Though generalized vesicular emphysema involves the entire lungs, the emphysema is usually most marked at the parts least supported during occasions of heightened intra-pulmonary pressure—*i.e.*, apices, anterior margins, lower and posterior margins (like the fur on a lady's mantle). It must not be forgotten that under ordinary conditions the lungs, far from being supported by the structure circumjacent to them, actually exercise suction upon them.

Owing to the loss of their elasticity, the lungs in generalized emphysema collapse but little when the thorax is opened, or when they are removed from the body. The anterior borders are found to have lost their sharp edges and to be rounded, showing emphysematous bullæ ('frog's lung'). They may also overlap in front and by covering the heart obliterate the area of superficial cardiac dullness.

The pulmonary tissue is pale and bloodless, pits more easily, and feels like eider-down. The air can be squeezed from one part to another with greater facility than under normal conditions.

As the emphysema progresses, the obstruction to the pulmonary circulation resulting from obliteration of the capillaries causes the branches of the pulmonary artery to dilate, and its main trunk often to become atheromatous. *Eventually the right heart becomes dilated*, and general venous congestion supervenes (enlargement of liver, œdema of lower extremities, and albuminuria).

Bronchiectasis.

In this condition there is permanent distension of the bronchi, which in consequence may be either—

(*a*) Cylindrical,
(*b*) Fusiform, or
(*c*) Saccular.

The pathology is much the same as that of emphysema —viz., increased stretching of the bronchial walls from augmented internal pressure (an unimportant factor), or increased traction from without. In bronchiectasis, however, another factor comes into operation—*i.e.*, weakening of the bronchial walls from degeneration of their muscular fibres, which by their active contraction must tend to prevent stretching.

Bronchiectasis is the usual accompaniment of all chronic diseases of the lungs, and is *found, typically developed, in fibroid phthisis.* In this disease the contraction of the fibrous tissue, attached to the adherent pleura on the one hand and the bronchi on the other, has been held to be an important factor in causing the dilatation. The real traction, however, comes from the powerful action of the inspiratory muscles, which, in accordance with the principle already mentioned, are in dyspnœa continually striving to increase the mean size of the chest. Were the normal amount of vesicular structure present without any fibrosis, such inspiratory action would lead to emphysema, with little or no dilatation of the bronchi, because the delicate vesicular walls would necessarily yield before the stouter bronchi. When, however, the lungs are seamed with con-

paratively non-yielding fibrous tissue, the effect of the constant inspiratory efforts will be to expand the bronchi as well as the vesicles.

The muscular coat of the dilated bronchi is in large measure replaced by a fibrous tissue, and the mucous membrane tends to lose its sensibility. As a result, the secretion of the tubes is apt to accumulate and to undergo putrefaction, not being expelled until it reaches a level at which the mucous membrane is sufficiently sensitive to be capable of exciting the act of coughing.

Pneumonia.

There are two classical forms of acute pneumonia, which run different clinical courses, present different pathological appearances, and have different exciting causes. These are—

(i.) Lobar pneumonia, and
(ii.) Lobular pneumonia.

(i.) **Lobar Pneumonia (Croupous).** — *The pneumococcus of Fraenkel is the essential cause*, though occasionally the pneumo-bacillus of Friedlander, streptococci, and staphylococci are also present. The pneumococci are constantly found in large numbers in the mouth, pharynx, and nasal cavities of man in health, and it is only when vitality is depressed (*e.g.*, by alcohol) that they can set up inflammation of the lungs. They are most numerous in the advancing area of disease. The constitutional symptoms are the result of absorption of the *pneumo-toxin* into the system.

The lesion usually begins at the base of one lung, and in typical cases involves the whole of a lobe in a uniform manner.

Lobar pneumonia is *always a pleuro-pneumonia*, and passes through the following stages :

The Stage of Congestion.—The affected area of lung is swollen, of a deep red colour from vascular engorgement, and less crepitant and less elastic to the feel than normally. It floats in water. The capillaries in the alveolar walls are distended, the lining endothelial cells swell up, and exudation of inflammatory lymph begins. Signs of pleurisy are evident.

The Stage of Red Hepatization.—The inflamed portion of lung is now solid, like a piece of liver; the inflammatory lymph has completely filled the alveoli and undergone coagulation, the clot being composed of a fibrinous network in the interstices of which are leucocytes, chromocytes, and shed endotholial cells. In consequence of this the inflamed lung is distended, and its pleural surface may be marked by the ribs. (This is probably a post-mortem phenomenon, as during life tho inspiratory muscles enlarge the chest on the affected side, and thus protect the inflamed lung from pressure.) The affected tissue does not crepitate, is very friable, and sinks in water. On section it looks like red granite, being dry and granular.

The Stage of Resolution may now occur, in which case the coagulum disintegrates, to be in part absorbed by the lymphatics and in part removed by expectoration; or, instead of resolution taking place at this period of the disease, the inflammation may pass on to

The Stage of Grey Hepatization.—The lung remains solid, is still more friable than in the second stage, and sinks in water. On section it looks like grey granite and may yield a puriform fluid. The fibrinous network has now dissolved, the chromocytes have disappeared, and the alveoli are packed with leucocytes.

If at this stage a section of the lung is made from apex to base, the organ will be seen to be mapped out into zones. At the bottom is the zone of grey hepatization, while above this are three others—first, a zone of red hepatization, above that a zone of congestion, and above that, again, a zone of œdema.

Abscess.—In some cases of pneumonia the alveolar walls disintegrate, leaving a cavity filled with dead leucocytes.

Gangrene.—In persons whose tissues are very much weakened by, *e.g.*, alcoholism, the intensity of the inflammation may be such as to cause gangrene.

Complications.—The pneumococci entering the circulation may set up pericarditis, malignant endocarditis, meningitis, or synovitis. The pleurisy may pass on to empyema.

The absence of leucocytosis in pneumonia usually

means a fatal termination. The expectoration of prune-juice-coloured sputum is also a bad sign, as it indicates much pulmonary œdema. At the time of the crisis the opsonic index undergoes a marked rise.

Chronic Pneumonia.—In rare cases the process becomes chronic; the alveolar walls become infiltrated with small round cells, which organize into fibrous tissue. The result is an induration of the affected portion of lung, with which is apt, in course of time, to be associated emphysema and bronchiectasis.

(ii.) **Lobular Pneumonia (Catarrhal, Broncho-Pneumonia).**—This disease is *always preceded by a preliminary capillary bronchitis*, of which it is the direct outcome.

It is microbic in origin, and an example of point-to-point infection. Thus, it occurs in children as the result of measles, whooping-cough, and scarlatina, and in adults after influenza and operations on the mouth and windpipe. The inspired air, rendered septic by passing over the infected mucous membrane of the mouth, nose, or pharynx, sets up a capillary bronchitis; subsequently, patches of pneumonia develop around the affected bronchioles, in consequence of—

(*a*) Direct extension of the inflammation; or

(*b*) Inoculation with septic material from the bronchioles; or

(*c*) Collapse of the alveoli from plugging of their bronchioles with mucus and subsequent absorption of the imprisoned air.

Possibly all these factors co-operate.

A section of such a lung will show in an early stage of the disease small, dark red, ill-defined patches, ranging in size from a pin's head to a pea, separated by healthy intervening lung tissue. At a later stage neighbouring patches may coalesce and a large and continuous area of consolidation result. Pleurisy is less common than in lobar pneumonia, and is found only in those cases in which the patches lie adjacent to the surface.

The bronchioles are inflamed, and filled with mucus and shed epithelium. The air vesicles are packed with cells—chiefly swollen endothelial cells—also leucocytes in variable numbers, and a few chromocytes. In some of the alveoli a fibrin network may be present.

Pulmonary Tuberculosis.

The term 'phthisis' is used as synonymous with pulmonary tuberculosis. Broadly speaking, there are four chief types :

(i.) Chronic or ordinary phthisis.
(ii.) Acute phthisis.
(iii.) Acute miliary tuberculosis.
(iv.) Fibroid phthisis.

(i.) **Chronic Phthisis.**—This is the ordinary form of pulmonary tuberculosis. Tubercles form in the *peri-vascular, peri alveolar*, and *peri-bronchial* lymphatics of the apex, and catarrhal pneumonia is set up in the immediate neighbourhood of the tubercles. This combined process is known as *consolidation.* The tubercles cascate, and thus the pulmonary tissue breaks down. This event is known as *excavation*, and the cavity formed is called a *vomica.* The chronic inflammatory process in the neighbourhood of the tubercles causes *fibrosis.* The pleura over the tubercular part thickens, and there is a bronchitis of the tubes leading to the affected area.

Should the disease now be arrested, the connective-tissue growth continues, until at length the cavity is sealed up by fibro-cicatricial tissue enclosing calcareous matter.

If, on the other hand, the disease progresses, fresh areas of the lung tissue are infected in succession, the processes of consolidation, excavation, and fibrosis are repeated again and again, and sooner or later the other lung becomes similarly affected.

Recently formed cavities have irregular walls of softened necrotic tissue, while old ones are lined with a smooth pyogenic membrane, often darkly pigmented. They contain pus, degenerated endothelial cells, lung debris, and caseous matter.

If a branch of the pulmonary artery passes along the wall of a cavity or across its lumen it is generally obliterated by thrombosis. Sometimes, however, there is no thrombosis, and under these circumstances an aneurism may form on the vessel, and by rupturing give rise to severe even fatal, hæmorrhage.

(ii.) **Acute Phthisis (Galloping Consumption).**—This is a form of pulmonary tuberculosis that runs a very rapid course, the patient dying within a few months.

Tubercles develop in the lungs and set up consolidation. The consolidated patches then break down and cavities form, the interior of which consist of softened, necrotic, and caseous material, with little tendency to the formation of an organized wall. In this way successive areas of pulmonary tissue are rapidly affected. If a cavity lies close to the surface it may ulcerate into the intra-pleural space, and cause *pneumothorax* and *pyopneumothorax*, no time having been allowed for pleural adhesion.

(iii.) **Acute Miliary Tuberculosis.**—In this disease an eruption of innumerable tubercles occurs throughout the substance of both lungs. It is probably never primary, *but always a final stage of a pre-existing tubercular lesion.* In this sense it is an auto-infection, the source of infection being, as a rule, caseating bronchial glands in the case of children, and in the case of adults an old tubercular deposit in the apex of one lung.

In acute miliary tuberculosis the bacilli are thought to be *carried by the blood-stream*, thus differing from other forms of tuberculosis, in which infection is conveyed by the lymphatics. The bacilli reach the blood either by the caseation of a gland into the walls of an adherent vein, or by the caseation of a tubercle which has formed on the outside of a bloodvessel. The bacilli cannot multiply while in the circulation, but only after coming to rest in some organ.

Patches of catarrhal pneumonia are scattered throughout the lungs, but death occurs before any marked destruction of tissue can take place. Many other organs may be affected simultaneously with the lungs.

(iv.) **Fibroid Phthisis (Cirrhosis of the Lung)** is a very chronic form of pulmonary tuberculosis, not usually developing until after the age of thirty, and lasting from ten to twenty years.

Fibrosis predominates over necrosis, the lung tissue being replaced to a greater or less extent by dense connective tissue, embedded in which are tubercles. *This form of phthisis is always associated with bronchiectasis*, the bronchiectatic cavities consisting either of dilated bronchi or being formed of broken-down lung tissue.

Gangrene of Lungs Causes:-(1) Irritation of foreign bodies (2) Insufflation of juices of ulcers. (3) Stagnation of fluid in cavities (4) Zymotic diseases e.g. Typhoid.

In a fully-developed case the lung is shrunken, hard, and fibrous, the pleura is thickened and adherent, and the organ feels like a cirrhotic liver. On section the fibrous tissue is found to have penetrated both the alveolar walls and the interlobular septa, obliterating many of the air-vesicles. There is marked dilatation of the bronchi, which often open into spaces lined by a smooth pus-secreting membrane. The pleura outside these bronchiectatic cavities is flattened, for bands of fibrous tissue pass to it from the walls of the cavities, and by contracting cause depression of its surface (see Bronchiectasis).

Pneumokoniosis (*konis*, dust).

This is a form of chronic interstitial pneumonia set up by the inhalation of irritating particles—coal-dust in miners (*anthracosis*), metal-dust in needle-and-knife grinders (*siderosis*), stone-dust in stonemasons (*silicosis*). Bronchial catarrh, patches of chronic catarrhal pneumonia, an increase—sometimes considerable—of the fibrous tissue, pigmentation, pleural adhesions, and bronchiectasis, are the notable pathological features. These cases are very liable to be complicated by tubercle, and are then examples of fibroid phthisis.

TUMOURS.

A tumour neoplasm is a local increase of growth leading to the formation of a mass of new tissue, more or less sharply differentiated from the surrounding tissue and subserving no useful purpose.

Tumours are of two chief kinds—the *innocent* and the *malignant*.

An *innocent tumour* is one which resembles more or less completely the tissue of the part from which it grows; it is usually circumscribed and encapsuled, does not recur after removal nor reproduce itself in distant parts.

A *malignant tumour* is one which tends to recur after removal, and to reproduce itself in distant parts. It tends to invade the surrounding tissues irregularly, so that there is no sharp division between the two, encapsulation taking place only exceptionally.

The ability of a malignant tumour to reproduce itself in distant parts depends—

1. Upon the fact that the characteristic cells of the tumours are not fixed but more or less loose, and thus free to be conveyed to distant parts by the lymphatics or bloodvessels; such loose cells can either pass straight into the lymphatics, which are continuous with the intercellular spaces throughout the body, or enter an ulcerated or ruptured bloodvessel. That the characteristic cells of malignant tumours are actually carried away to secondary sites, thereby producing the secondary growths, is proved by the fact that malignant tumours *always breed true*; a squamous epithelioma of the tongue produces a similar growth in the local lymphatic glands, which normally contain no epithelial cells; a giant-celled sarcoma of the testis causes giant-celled sarcoma of the lungs.

In the innocent tumours, as in the case of normal tissues, all the cells, other than the blood cells, are fixed; the connective tissues form a fixed framework, in the meshes of which the parenchyma cells are kept *in situ*.

2. Upon the fact that the malignant tumour cell, after its lodgment in a distant tissue, is able to multiply there and breed a colony of new cells. It is very doubtful if a cell of a normal tissue—say the liver—even if it became detached and conveyed to a distant tissue, could survive in its new habitat, much less multiply and form a new tissue. Clearly, the malignant cell is not only possessed of great vitality, but has great capacity for multiplying, and is able, both in its primary site and when carried to a secondary site, to grow at the *expense of the normal tissue*.

This quality of rapid proliferation may be innate in the malignant cell, just as it is in embryonic cells, or it may be the result of some irritant acting upon the malignant cell. A microbe dwelling in the interior of a carcinoma cell might conceivably provide the necessary stimulus in the case of the carcinomata. But microbe or no microbe, it is certain that some irritant is at work, as shown by the changes which take place in the normal tissues at the confines of the tumour. These changes are strongly suggestive of a toxic irritant.

Embryologically, tumours may be classified as follows:

Embryological Classification.

- Mesoblastic, or connective tissue
  - Non-malignant
    - Myxoma.
    - Fibroma.
    - Papilloma.
    - Glioma.
    - Lipoma.
    - Chondroma.
    - Osteoma.
    - Odontomes.
    - Neuroma.
    - Myoma.
    - Angeioma.
    - Lymphangeioma.
  - Malignant
    - Sarcoma.
    - Endothelioma (?).
- Epiblastic epithelial
  - Non-malignant—Adenoma.
  - Malignant—Carcinoma.
- Hypoblastic epithelial
  - Non-malignant—Adenoma.
  - Malignant
    - Columnar-celled carcinoma.

Teratomata—Dermoid.

A **Myxoma** is composed of stellate connective-tissue cells, which by the union of their processes form a delicate network, within the meshes of which is a clear mucoid material containing a small number of round cells. The tumour thus resembles in structure the vitreous humour of the eye and the Whartonian jelly of the umbilical cord.

Sites. — Subcutaneous tissues, the bladder, rectum, nerves, and spinal cord. A myxoma may also occur in association with cartilaginous tumours of the parotid and the testicle, and sometimes in connection with sarcomata.

A **Fibroma** is a tumour composed of connective-tissue cells and white fibres arranged in wavy bundles. It is round or lobulated in form, and generally enclosed in a distinct capsule. On section, and viewed obliquely, it looks like 'watered silk.'

Fibromata may be *hard* or *soft*, according as the elements composing them are loosely or closely packed.

Sites.—The hard fibroma is met with on the gums (fibrous epulis); the soft fibroma, in the skin, as a pedunculated mass (molluscum fibrosum). Other situations are: Fasciæ, tendon sheaths, periosteum, base of skull, nerves, and uterus.

The so-called 'mucous polypus' of the nose is an œdematous soft fibroma.

Most so-called *neuromata* are in reality fibromata involving nerve trunks.

A **Papilloma** (sometimes classed as an epithelial tumour) consists of a main stalk of connective tissue, giving off primary and sometimes secondary processes, the whole being capped by the normal epithelium of the part. This, however, *never invades the underlying tissue* (thus differing from carcinoma).

The connective tissue of papillomata is more cellular than normal connective tissue, being sometimes even myxomatous, and the bloodvessels are more dilated. In certain situations—*e.g.*, the bladder—papillomata are prone to bleed.

Sites.—The skin (warts), larynx, rectum, bladder.

A **Glioma** is a tumour growing from the delicate connective tissue (*neuroglia*) of the nervous system, and not sharply demarcated from the surrounding parts. It is soft and in appearance translucent, not unlike the grey matter of the brain.

Structurally it consists of a large number of closely packed stellate cells, with numerous branching processes which interlace to form a network. It is often very vascular, and the vessels, having thin walls, are liable to rupture; hence *the frequency of hæmorrhages within it.* It is non-malignant, and dangerous only on account of the pressure it exerts.

Sites.—Brain, spinal cord.

The so-called *glioma of the retina* contains, besides the ordinary cells, others which resemble epithelium, and for this reason the growth is sometimes classed among the epithelial tumours. It is liable to extend along the optic nerve and to recur after removal. It occurs most frequently in young children.

A **Lipoma** is composed of ordinary adipose tissue. It is the commonest of all the tumours in man, and may attain to an enormous size (60 pounds). It may be either *circumscribed* or *diffuse.*

A *Circumscribed Lipoma* (the usual kind) is a rounded, lobulated tumour of elastic or doughy consistency, contained within a distinct capsule. It is generally single, but two, ten, or more may coexist.

Sites.—The common situation is in the subcutaneous tissues; but it may occur in the subserous tissues (peritoneum, pleura), in the subsynovial and submucous tissues, between or in muscles, in the periosteum, and in the meninges of the brain and spinal cord.

A *Diffuse Lipoma* is a diffuse symmetrical overgrowth of subcutaneous adipose tissue, not encapsuled, generally occurring beneath the chin or at the back of the neck. It is said to be most frequently met with in beer-drinkers.

A lipoma may contain other tissues besides fatty. Examples of such are myxo-lipoma, fibro-lipoma, nævo-lipoma.

Xanthoma.—This is a modified form of lipoma, its substance resembling embryonic fatty tissue, with an admixture of small round cells. It occurs on the eyelids in the form of flat elevations of a yellow colour. It may also be found in diabetes (but rarely on the eyelids or face).

A **Chondroma** is a tumour composed mainly of hyaline cartilage, though it may also contain a certain amount of fibro-cartilage. It may consist either of a single mass of cartilage or be composed of lobules bound together by a vascular fibrous tissue. Ossification and calcification are exceptional.

Sites.—The most common situation of chondromata is the interior of the phalanges of the hand, where they are often multiple. They are only found in the bones which develop from cartilage, and they probably originate either from misplaced islets of cartilage or from the epiphyseal cartilage.

Chondromata also occur in the *parotid gland* (where they probably originate from Meckel's cartilage) and in the *testis;* but in these situations the tumour is generally associated with myxomatous or sarcomatous elements (or both). Pure chondroma of the testis is exceedingly rare.

An **Osteoma** is a tumour composed of bone tissue. There are two chief varieties: (*a*) Cancellous, or spongy; and (*b*) compact, or ivory.

(*a*) *Cancellous.*—This is usually met with as a pedunculated, 'cauliflower' mass of about the size of a walnut, attached to the end of a long bone.

It appears to originate from the epiphyseal cartilage, and consists of a mass of spongy bone limited by a shell of compact bone. During the period of its development the tumour is encased in a thin layer of hyaline cartilage, and it is by the ossification of this that increase of size takes place. When the epiphysis becomes united to the diaphysis, growth ceases and the tumour remains stationary.

Sites.—Lower end of femur, ungual phalanx of great toe, upper ends of tibia and humerus. Sometimes the tumours are hereditary and multiple.

(*b*) *Ivory.*—This is composed of very dense bony tissue, of the consistence of ivory. It is rounded in form and usually sessile.

Sites.—Although a tumour of this variety may develop on any bone, its most frequent sites are: Frontal sinus, orbit, external auditory canal, angle of the lower jaw, mastoid process, ilium, and scapula.

Odontomes (Tooth Tumours).—'Odontomes are tumours composed of *dental tissues* in varying proportions and different degrees of development, arising from teeth germs or teeth still in the progress of growth:

'Epithelial odontomes, from the enamel organ.
'Follicular odontomes
'Fibrous odontomes
'Cementomes (unknown in man)
'Compound follicular odontomes } from the tooth follicle.
'Radicular odontomes, from the papilla.
'Composite odontomes, from the whole germ' (Bland-Sutton).

Epithelial Odontomes (*Multilocular Cystic Tumours*) are composed of a number of small cysts lined by cubical epithelium, and embedded in a fibrous stroma. They contain a viscid fluid, and appear to originate in branching columns of epithelial cells derived from the enamel organ, which cells break down in their more central parts. The jaw becomes expanded, but growth is slow. These cysts are non-malignant, showing no tendency to affect the glands or to disseminate.

Follicular Odontomes (='dentiferous cysts') are cysts which form in connection with misplaced and non-erupted teeth. The expanded dental sac represents the cyst wall. The interior contains a viscid fluid and the crown of the non-erupted tooth, the fang of which is usually fixed to the cyst wall, though sometimes the tooth is loose. With rare exceptions, follicular odontomes form only in connection with the *permanent* teeth,

and more particularly with the canine of the upper jaw. The tumour grows slowly. Owing to expansion of the surrounding bone, 'egg-shell crackling' may in course of time be felt on pressure. (These cysts must be distinguished from 'dental cysts' which develop from the fangs of normally erupted teeth.)

Fibrous Odontomes also occur in connection with non-erupted teeth. The dental sac thickens and forms a capsule, which by enclosing the tooth prevents its growth. The capsule is composed of laminated fibrous tissue containing calcareous matter.

(*Cementomes* are unknown in man, but are met with in horses. The dental sac undergoes calcification, so that the tooth lies enclosed in a capsule of hard cement.)

Compound Follicular Odontomes are of very rare occurrence. 'When the thickened capsules of one or more unerupted teeth become confluent and ossify sporadically, a tumour is produced containing one or more denticles and fragments of cementum. Such tumours are known as compound follicular odontomes' (Bland-Sutton).

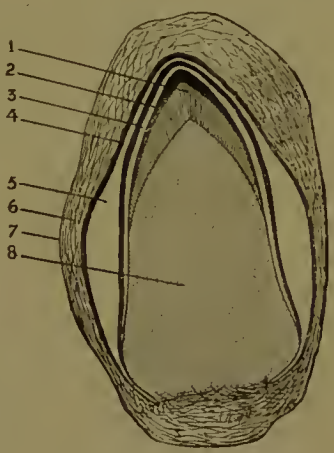


FIG. 4.—DIAGRAM OF DEVELOPING TOOTH.

1, Dentine; 2, enamel; 3, inner layer of epithelium of enamel organ; 4, outer layer of epithelium of enamel organ; 5, gelatinous tissue; 6, inner layer of dental sac; 7, outer layer of dental sac; 8, dental pulp (Thiersch).

Radicular Odontomes are very rare in man. They grow from the *roots* of a tooth, and consist of dentine and cement in varying proportions. The crown of the affected tooth is normal.

Composite Odontomes consist of heterogeneous masses of dentine, enamel, and cement indiscriminately blended together, and having but little resemblance in shape to teeth. In the majority of cases two or more teeth are fused together. Composite odontomes grow from within, expanding the bone. They are very rare.

The term **Neuroma** is used to indicate any tumour growing from a nerve. A true neuroma composed of nerve elements alone is exceedingly rare.

A *Neuro-fibroma* consists of bundles of nerve fibres,

together with a varying amount of connective tissue, the whole being enclosed within a distinct capsule. It is often multiple, and is very liable to myxomatous degeneration.

A *Plexiform Neuroma* consists of a plexus of thickened, tortuous strands of nerve tissue embedded in a large quantity of myxomatous tissue. As a rule it is congenital.

An *Amputation Neuroma* is the 'bulb' which forms on the proximal end of a nerve after its division, and on nerve ends in amputation stumps. It consists of coiled-up, newly-formed nerve fibres embedded in fibrous tissue. If adherent to the cicatrix, or bone, it may cause severe pain.

A **Myoma** is a tumour composed of muscle tissue. Two varieties occur: the (*a*) rhabdomyoma, consisting of striated muscle; and the (*b*) leiomyoma, consisting of non-striated muscle.

The *Rhabdomyoma* is a very uncommon type. Its usual seat is the kidney. The component elements rarely present the characteristics of normal striated muscle, but consist chiefly of spindle-shaped cells, together with a large number of embryonic cells and only a few striated fibres.

The *Leiomyoma* only develops *from pre-existing unstriated muscle fibre*, and is most common as the 'uterine fibroid'; but it occasionally occurs in the œsophagus, stomach, intestines, and prostate. It has also been found in connection with the broad ligaments and the ovaries.

When occurring in the uterus, this tumour is composed of bundles of spindle-shaped unstriated muscle fibres, which interlace in various directions. In places the fibres are arranged concentrically, presenting the appearance of tiny balls of cotton. There is generally a fair amount of fibrous tissue present, so that the tumour is often called a *fibro-myoma*.

The **Angeiomata** are tumours composed of dilated bloodvessels. They are of three kinds—

(*a*) Simple nævus.
(*b*) Cavernous nævus.
(*c*) Plexiform angeioma.

(*a*) A *Simple Nævus* consists of a mass of dilated capillaries and venules held together by connective tissue.

It is nearly always congenital, and usually tends to increase in size for a few months after birth.

(*b*) A *Cavernous Nævus* resembles in structure the corpus cavernosum of the penis, and consists of a series of inter-communicating spaces the walls of which are lined by endothelium, and embedded in a fibrous stroma. Small arteries open directly into these spaces, and veins carry the blood away.

The tumour may be provided with a distinct capsule, or it may merge gradually into the surrounding tissue.

It may be congenital, but more frequently it develops in later life.

Sites.—Skin of face, trunk, limbs, and liver.

(*c*) *Plexiform Angeioma.* — When a single artery becomes dilated, thinned, elongated, and tortuous—resembling a varicose vein—the condition is known as *arterial varix.* When the same condition affects several neighbouring arteries, it is known as *cirsoid aneurism.* If the dilatation involves the capillaries and veins as well, with the formation of a pulsating, bluish, spongy tumour, the condition is termed *plexiform angeioma.*

Sites.—May be found on any part of the body, the usual seat being the scalp, where it affects the temporal, posterior auricular, and occipital arteries.

A **Lymphangeioma** is a tumour composed of dilated lymphatics, associated with hypertrophy of their walls and atrophy of the intervening tissue. The dilatations may be so extreme as to constitute actual cysts. Three kinds are described—(i.) *Lymphatic nævus* (occurring in the skin and tongue); (ii.) *cavernous lymphangeioma;* (iii.) *lymphatic cyst* (occurring in the neck, axilla, chest wall, and always congenital).

Sarcomata.

Sarcomata are malignant tumours composed of *embryonic* connective tissue (mesoblastic). Broadly speaking, *the more embryonic the cells, the more malignant is the growth,* and *vice versa.* There would appear to be some misdirection of cellular activity — proliferation instead of development into adult tissue.

Structure.—The characteristic cells are nucleated round cells (large and small); nucleated spindle cells (large and

small), and multi-nucleated giant cells. *Inter-cellular substance* is always present, but though very evident in some cases, it is difficult to distinguish in others. It may be fluid and homogeneous, granular or finely fibrillated, and sometimes cartilaginous or osseous.

The bloodvessels are usually very numerous, and generally embryonic in structure. Often they are mere channels or spaces between the cells of the tumour. This explains the frequent occurrence of hæmorrhage into the substance of the growth; also the way in which tumour cells can be carried into the circulation and deposited in distant organs, there to set up secondary growths.

Mode of Spreading.—Sarcomata infiltrate locally. At the growing border of the tumour there is a great excess of small round cells. These advance in all directions, absorbing the normal tissues (muscles, glands, etc.) in their immediate vicinity.

The most common channel of dissemination is the *blood-stream.* Detached groups of the cells pass into the circulation, and are carried by the veins into distant organs (notably the lungs), there reproducing the structure of the original growth.

Melanotic sarcoma, sarcomata of lymph glands, tonsil, thyroid, testis, as likewise all quickly-growing sarcomata, *spread by the lymphatics as well as by the blood-stream.*

The classification of sarcomata is based upon the prevailing type of constituent cell:

(i.) Round-celled—
  (*a*) Small; (*b*) large.

(ii.) Spindle-celled—
  (*a*) Small; (*b*) large.

Special forms—

(i.) Lympho-sarcoma.
(ii.) Myeloid.
(iii.) Alveolar.
(iv.) Melanotic.
(v.) Myxo-sarcoma.
(vi.) Chondro-sarcoma.
(vii.) Osteo-sarcoma.

Small-round-celled Sarcomata are the commonest form of sarcoma, and, next to the melanotic, the most malignant. They grow rapidly, infiltrating the surrounding tissues, often attaining a great size, and disseminate through the bloodvessels. They are encephaloid in appearance, being to the naked eye very like the encephaloid carcinoma.

Sites.—They may occur in any organ: in the bones, glands (especially the mamma and testis), muscles, and subcutaneous tissues.

Large-round-celled Sarcomata are rarer and less malignant than the last-named variety. The cells are large, and have a round and distinct nucleus.

Spindle-celled Sarcomata consist of oat-shaped or fusiform cells, tapering to a point which often bifurcates. They are arranged in bundles, which take different directions, so that in section under the microscope some of them appear rounded and others spindle-shaped.

They are firmer than the round-celled sarcomata, and they may contain an admixture of myxomatous tissue (*myxo-sarcoma*), cartilage (*chondro-sarcoma*), and bone (*osteo-sarcoma*). In slow-growing forms some of the spindles may be converted into fibrous tissue (*fibro-sarcoma*).

Sites.—Bones, subcutaneous tissues, fasciæ.

The **Lympho-Sarcomata** are composed of cells identical with those of the round-celled sarcomata, and they contain a delicate, fibrillated, inter-cellular substance.

Sites.—Their common seat is in the bronchial and mediastinal lymphatic glands, but they are also found in the mesenteric and other lymphatic glands.

Myeloid Sarcomata grow from the marrow and absorb the bone around. As the result of irritation, new bone is laid down from the periosteum, and this, expanding from pressure and thinning out, gives rise to the characteristic 'egg-shell crackling' when pressure is made.

In appearance, the cut surface often suggests a piece of liver, owing to the presence of extravasated blood which has undergone pigmentary changes. Cysts are common.

The cells composing this tumour are of two kinds—(*a*) *Spindle cells*, which form the bulk of the growth and (*b*) *multinuclear giant cells*, scattered throughout.

The *giant cells* are large, irregularly spheroidal, and generally without processes. *The nuclei are scattered throughout the cell contents*, not concentrated at the periphery, as in the giant cells of tubercle.

The tumour is often *very vascular*, so that it may pulsate, and thus be mistaken for an aneurism. Secondary growths are exceedingly rare, so much so that some pathologists would assign to them a separate class—the myelomata.

Sites.—The lower end of femur, upper end of tibia, upper end of humerus, and the lower jaw.

Alveolar Sarcomata, which are very rare, grow from the skin. Their round or oval cells are grouped in alveoli formed by fibrous tissue. Between the cells is a delicate, fibrillated, inter-cellular substance.

Melanotic Sarcomata contain an *intra-cellular* pigment (melanin), elaborated by the cells themselves and differing in composition from the ordinary blood pigments in containing sulphur, but usually no iron. An iron-containing pigment may, however, sometimes be found *between* the cells as the result of blood extravasation.

Some of the cells are spindle-shaped and others epithelioidal, and they are sometimes contained in alveoli, as in the alveolar sarcoma. When a melanotic sarcoma grows from the skin, the alveolar structure with epithelioid cells is the rule, and accordingly some pathologists regard this form as a carcinoma.

Although locally far less malignant than many other kinds of sarcomata, the melanotic sarcomata are the most malignant of all tumours on account of their rapid dissemination. Thus, by the time the primary growth has reached the size of a filbert, secondary growths are to be found in the lungs, liver, kidneys, and brain. *They disseminate by the lymphatics as well as by the bloodvessels.*

Sites.—The primary seats are the tissues which normally contain pigment—*i.e.*, the skin and the uveal tract of the eye (iris and choroid).

The **Osteo-Sarcomata**, as primary growths, are met with almost exclusively in bone. As a rule, *calcification* is more common in them than true ossification, but spicules of true bone can generally be detected.

Endotheliomata.

The **Endotheliomata** are tumours growing from the endothelium of serous membranes (pleura, peritoneum, meninges of brain, etc.), lymphatics, bloodvessels, and sometimes from the parotid gland, testicle, and ovary. The cells are large, round, and sometimes 'epithelioid' in shape, with no inter-cellular substance, and they are contained in alveoli formed by fibrous tissue. The structure of the endotheliomata thus resembles that of the carcinomata.

The endotheliomata, as a rule, develop slowly; they are but slightly malignant, secondary growths being rare.

Psammomata are endotheliomata which grow from the pia mater of the brain and the choroid plexuses. The cells, usually containing calcareous granules, are arranged in groups lying in a fibrous stroma. In the brain a psammoma rarely exceeds the size of a shelled walnut.

Non-malignant Epithelial Tumour.

The **Adenomata** are new formations of gland tissue arising in connection with, and constructed on the model of, the secreting gland from which they grow, but their ducts do not enter those of the gland, and they contribute nothing to its physiological functions.

Imitating the structure of the gland from which it springs, an adenoma consists, when growing from a compound tubular gland, of acini and ducts, and, when growing from a simple tubular gland, of tubules. The acini and tubules alike are lined by regular epithelium, *which does not infiltrate into, and is sharply demarcated from, the surrounding tissue.*

The connective-tissue stroma varies in amount. In some cases this is so considerable that the growth is called an *adeno-fibroma*. In the quickly-growing forms myxomatous and sarcomatous elements may be intermingled with the stroma. Such mixed forms are known as *myxo-adenoma*, *sarco-adenoma*, etc. Further, the tubes and acini may become distended into cysts forming a *cysto-adenoma*, and occasionally the stroma may project into the lumen of the acini, when the growth is called a *papillary adenoma*.

Adenomata are generally encapsuled and not infre-

quently multiple. They never reproduce themselves in distant organs.

Sites.—Mamma, thyroid, ovary, intestine, and prostate.

Malignant Epithelial Tumours (Carcinomata).

It is well to call attention here to the fact that between the epithelium and the subjacent connective tissue of an organ there is a homogeneous layer—the *basement membrane*. This is generally formed of flattened connective-tissue cells joined edge to edge.

A **Carcinoma** is a malignant tumour which always develops in connection with pre-existing *epithelial* tissues (epiblastic or hypoblastic). It may be defined as a *malignant tumour consisting of aberrant epithelial tissue.*

The distinguishing characteristic of this tumour is the practically *unlimited power of multiplication possessed by the epithelial cells*, which, breaking through their normal boundaries, invade the surrounding tissues. These cells, following the paths of least resistance, tend to travel along the lymphatic clefts, pushing aside the connective tissue. This latter, reacting to the stimulus, proliferates, so that we have ultimately a tumour composed of a fibrous stroma circumscribing groups of epithelial cells.

Fig. 5.—Stroma of Carcinoma (Cornil et Ranvier).

These cells tend to resemble those of the part from which they grow: thus, a carcinoma of the lip is built up of squamous cells; of the breast, of spheroidal cells; of the intestine, of columnar cells. From mutual pressure the cells may also become polymorphous. They are closely packed, and have no organized inter-cellular substance, and no bloodvessels running between them. *The bloodvessels are confined to the fibrous stroma.*

Inasmuch as the spaces into which the cells grow are simply dilated lymph spaces, it is easy to understand that carcinomata spread locally by lymphatic infiltration, and

that secondary growths from them tend first to infect the group of lymphatic glands nearest to and draining the carcinomatous area.

General Characters.—As a carcinoma is constantly infiltrating the tissues around, it is not encapsulated, and its outline is not sharply defined. Other features of carcinomata are: their great tendency to involve the superficial tissues, to undergo degenerative changes (*e.g.*, colloidal or fatty degeneration), to ulcerate, and to infect the neighbouring lymph glands. Secondary growths may, however, occur in any organ or tissue, including the bones; and such always reproduce the same type of cell as that of the parent tumour—*e.g.*, in carcinoma of the rectum the characteristic columnar cells of this part are to be found in the secondary nodules, whether they form in the liver, inside the shaft of a long bone, or elsewhere.

Carcinomata tend to reproduce themselves in distant organs, to recur after removal, and to give rise to a cachexia which is probably toxæmic in nature.

The cause of carcinoma is one of the mysteries of pathology. The only definite statement that can at present be made is that *irritation* seems to play an important part. Witness the usual sites—lips, tongue, œsophagus (at its beginning, end, and where it is crossed by the left bronchus), the two orifices of the stomach, cæcum, hepatic flexure, splenic flexure, sigmoid flexure, breast, and cervix of the uterus. Cancer of the small intestines—the contents of which are fluid—is a pathological rarity. Professor Fournier says that epithelioma of the tongue is but rarely found except in those who have syphilitic leucoplakia and who at the same time smoke in excess. Few syphilitics, however, who do not smoke ever develop lingual cancer, and still fewer cases are found in smokers who are non-syphilitic.

The classification of carcinomata is based upon the origin, character, and arrangement of the epithelium found in the tumours:—

- Epiblastic
  - Squamous epithelioma.
  - Rodent ulcer.
  - Spheroidal-celled
    - Scirrhus.
    - Encephaloid.
  - Duct cancer.
- Hypoblastic
  - Columnar-celled.
  - Colloid.

A **Squamous Epithelioma** grows from parts covered by stratified squamous epithelium (skin, mouth, tongue, pharynx, œsophagus, larynx, vulva, vagina, lower part of cervix uteri, penis, and anus). It first appears as a warty growth, which soon breaks down in the centre, forming an ulcer with very hard, raised, everted edge and indurated floor. There is a down-growing of the epithelium, branching columns of epithelial cells, derived from the rete Malpighii, forcing their way downwards through the tissues, like the roots of a tree through the soil, and becoming embedded in a stroma of fibrous tissue.

It is these ingrowing columns which, when viewed on transverse section under the microscope, constitute the so-called 'cell-nests.' These are onion-like masses of cells having the following structure: In the centre are flattened cells which have undergone mucoid and colloid degeneration; around these are layers of crescent-shaped cells, and on the outside columnar-shaped cells resembling those of the rete Malpighii. This order is explicable by the fact that the down growth of the epithelium is of the nature of an invagination. In course of time the whole cell-nest becomes a mass of flattened cells arranged concentrically around the colloid centre.

The group of lymphatic glands nearest the growth are soon infected, and in course of time may become cystic, involve the skin, and ulcerate. *No secondary growths occur beyond these lymphatic glands as a rule.*

A **Rodent Ulcer** is a species of epithelioma growing from the sebaceous glands, sweat glands, or hair follicles, and generally occurring above a line drawn from the angle of the mouth to the lobe of the ear. Common situations are the root of the nose and the neighbourhood of the eyelids. The growth begins as a small tubercle in the skin, which soon breaks down into an ulcer with a hard, raised, everted, sharply-cut sinuous edge and smooth, depressed floor. The disease extends very slowly, and may go on for many years, gradually destroying the tissues both superficially and in depth. In this way it may eat its way through bone and even the brain itself.

It is not uncommon for the ulcer to make abortive attempts at healing, but the scar tissue which forms soon breaks down.

Structurally a rodent ulcer resembles an ordinary epithelioma, but the individual cells are smaller, and in most specimens the cell-nests are absent, or, when present, ill-developed.

The lymphatic glands are not affected, and dissemination into distant organs never occurs.

Spheroidal-celled (or **Alveolar**) **Carcinoma** is the ordinary cancer of the breast. A fibrous tissue stroma encloses well-defined inter-communicating alveoli—whence the name 'alveolar' (see Fig. 5)—packed with epithelial cells, spheroidal or polygonal in shape. In course of time the growth invades the pectoral fascia and skin, eventually ulcerating on the surface.

There are two chief varieties, depending upon the ratio of cells to stroma. If the stroma is abundant, while the cells are not plentiful, the tumour is hard and is called *scirrhus;* if the stroma is sparse and the cells are abundant, the tumour is soft and is said to be *encephaloid.*

The area of infiltration of the tumour is usually much greater than the clinical signs would suggest.

In the case of scirrhus the primary growth may be small in comparison with the secondary growths, which are always of the encephaloid variety.

In mammary carcinoma the lymphatic glands in the axilla are soon infected, and the disease may spread to the mediastinal glands and other parts. As the lymphatics anastomose across the middle line of the chest, the glands in the opposite axilla are sometimes involved.

Duct Cancer (or **Villous Cancer**) grows from the epithelium of the ducts of the breast (generally not far from the nipple). It is composed of a fibrous stroma enclosing alveoli. The alveoli are lined with (*i.e.*, not entirely filled by) columnar epithelium, and into their interior project vascular papillary processes. Owing to the rupture of the bloodvessels in these processes, the alveoli often contain much extravasated blood, which may escape by the nipple.

Duct cancers are of slow growth, not so liable as other forms of carcinoma to affect the glands, and show less tendency to recur after removal.

Paget's Disease of the Nipple is a chronic form of eczema occurring on the nipple or areola. It is characterized by: resistance to treatment, tendency to ulceration, *and liability to be followed by carcinoma of the breast*—either in the immediate neighbourhood of the eczema or at a distance from it.

A **Columnar-celled Carcinoma** is a tumour growing from the positions where normally there are columnar cells—*e.g.*, the mucous membrane of the stomach, intestines, and uterus (body and upper part of cervix).

It consists of alveoli embedded in a fibrous stroma; but, instead of being packed with cells, as is the case with the ordinary epiblastic carcinoma, the alveoli are, as in duct cancer, *lined* with columnar epithelium, enclosing a central space, a columnar-celled carcinoma in this respect resembling an adenoma: hence the old name of *adenoid cancer* applied to it.

Fig. 6.—Columnar-celled Carcinoma.

It differs, however, from an adenoma in that it lacks definition, infiltrates the neighbouring tissues, ulcerates with extreme readiness, and gives rise to secondary growths.

Columnar-celled carcinomata show a marked tendency to *colloid* degeneration.

Colloid Cancer is simply one of the preceding forms, the epithelial cells of which have undergone colloid degeneration. This is common in the cancers of the stomach, intestines, and ovary.

Epithelioma of the Chorion (syncytioma malignum) is a variety of malignant tumour occurring during pregnancy. Originating in the placental site, it tends quickly to invade the walls of the uterus and neighbouring parts, and to reproduce itself in the lungs and less frequently in the liver, spleen, or other organs.

'The tumour is mostly composed of blood-clot, with comparatively small processes, composed of epithelial cells, towards its outer part, where it borders upon the inner wall of the uterus. Some of these have a more or less distinct tubular formation. The interior of many of the tubes shows an irregular space, which in a few is occupied by a fibrous tissue with bloodvessels. The most favourable of these tubes are easily recognized as villi, with a hypertrophied epithelial covering. The epithelial cells are arranged in the two layers typical of a villus—the outer syncytial and the inner polyhedral, or Langhan's, layer. The proportionate amount of these varies greatly in the different processes, the syncytial cells being usually fewest in the most typical villi. The fibrous tissue core of the villus tends to degenerate and disappear, and the empty, irregular, tubular spaces may be villi in which this change has taken place. It is possible also for the epithelial cells to aid in the absorption and disappearance of their own fibrous cores, in the same way as they cause the absorption of the tissues of the uterine wall. On the other hand, the evidence of the absorption of the uterine wall by the epithelial cells is very obvious. These cells are, however, mostly separated from the muscle fibres of the uterus by a protective fibrous tissue layer of new formation; and when the invading cells form an obvious villus-like process, representatives of both layers are seen in varying proportions, but where the invasion of the uterine wall is earliest, as in the thin, thread-like processes of cells, or in isolated individual cells, they are all apparently of a syncytial type. The walls of the uterine bloodvessels are directly invaded in the same way as other uterine tissues; hence the epithelial cells gain entrance into the circulation, and may be seen in greater or less numbers in many of the vessels with intact walls which lie at some distance from the tumour. Many of these cells may die, but others may survive and form the nuclei of new growths elsewhere in the uterine wall or in distant organs' (Leith).

The Incidence of Cancer in Relation to Sex and Situation.

On analysing 6,732 cases of cancer occurring at the Middlesex Hospital between the years 1746 and 1904, Dr. Lazarus-Barlow found that the mean age of incidence in males was 55·2 years, and in females 49·9 years. In males 80 per cent. of all cases of cancer occurred in the alimentary tract, while in females 80 per cent. were found in the generative organs and breasts. Cases of cancer of the alimentary tract were seven times as frequent in males as in females (see Fourth Report from the Cancer Research Laboratories, Middlesex Hospital).

After the age of thirty-five, one in eight females and one in twelve males die from carcinoma.

Cysts.

A cyst is a closed sac of abnormal development, the contents of which are fluid or semi-fluid.

The different varieties :

1. *Retention Cysts*, constituting the majority of cysts, and caused by obstruction to the outflow from a gland or cavity. Mucous, sebaceous, mammary, renal, thyroid cysts, and ranula, are examples. They are lined by a layer of epithelium.

2. *Cysts formed by the Dilatation of a Fœtal Tube which Normally is Obliterated—e.g.*, parovarian cysts, cysts in connection with the thyroglossal duct.

3. *Cysts containing an Animal Parasite — e.g.*, hydatid.

4. *Synovial Cysts*, resulting from hernial protrusions of the synovial membrane of a joint, and hernial protrusions of tendon sheaths (ganglion).

5. *Neural Cysts*, of which meningocele and spina bifida are examples.

6. *Cysts resulting from Degeneration in the central part of a tumour—e.g.*, in sarcomata.

7. *Hæmatomata.*

Teratomata.

The term *teratomata* (*teras*, a monster) is applied to tumours composed of an assortment of many different tissues mixed in varying proportions. Some contain dermal structures—*e.g.*, skin, nails, hair, and teeth (=dermoid cyst), and others may contain muscle, cartilage, bone, nerve, viscera, or, indeed, any tissue of the body. They appear to result from some congenital misdevelopment.

Dermoid Cysts occur most commonly in the ovaries, but also in the testicles, about the angles of the orbit, in the neck, and elsewhere. The cyst wall is composed of skin, and inside the cyst are hair, nails, or teeth, and sebaceous matter. In many cases they seem to result from inclusion of the epiblast during the closure of the embryonic clefts. In the case of the ovary, they probably either develop from the Wolffian body—an epiblastic structure—or result from the aborted local growth of an ovum.

DISEASES OF THE LIVER.

The liver is developed as a diverticulum of the primitive gut. The liver cells are hypoblastic, and the stroma mesoblastic, in origin. The organ is composed of lobules, each of which is about $\frac{1}{20}$ inch in diameter. Between the lobules is a supporting connective tissue carrying the lymphatics, bloodvessels, and bile-ducts. Within the lobules are the liver cells, closely packed, in form polyhedral from mutual pressure, and separated from one another by a sparse and very delicate tissue continuous with the interlobular connective tissue. The portal vein drains the blood from the capillaries of the alimentary mucous membrane, from the lower end of the œsophagus to all but the lower end of the rectum. It ends in the capillaries of the liver lobule, where a junction is effected with the capillaries of the hepatic artery.

The blood is carried *from* the liver lobule by the *hepatic system of veins*, and thence to the right heart. The portal circulation is peculiar in that it begins and ends in capillaries, and is destitute of valves. With the solitary exception of fat, all the substances absorbed from the gastro-intestinal tube pass into the portal system, and have to be subjected to the influence of the liver before they can enter the general circulation. In addition to its many other functions, the liver is a great blood-purifier or de-toxinator.

For pathological purposes the liver lobule may be divided into three zones. Fatty degeneration begins in the outer zone, amyloid disease in the intermediate zone, and 'nutmeg' liver in the central zone.

Jaundice.

Jaundice is a condition in which the bile enters the general circulation, and stains yellow the fluids and tissues of the body. The view now held is that its cause *in all cases is some obstruction to the outflow of bile into the duodenum*, in consequence of which it is first absorbed by the lymphatics, and then passes into the blood-stream through the lymphatic duct. *Ligature of the thoracic duct prevents jaundice.*

The obstruction may arise from catarrh of the bile-ducts, gall-stones, malignant disease of the liver or pancreas, etc.

Chronic Venous Congestion ('Nutmeg Liver').

This condition is caused by obstruction to the free flow of the blood from the hepatic veins, the obstacle being generally due to chronic valvular disease of the heart, or to primary obstruction in the pulmonary circuit, as from emphysema of the lungs or fibroid phthisis.

A fact to bear in mind in connection with this disease is that no valves intervene between the central intra-lobular hepatic vein and the right heart. Thus, in mitral regurgitation—*e.g.*, when compensation fails—the 'back-wash' from the left heart will produce its effects first on the lungs, then on the right heart, and then very readily upon the valveless hepatic veins. (These mechanical effects of pressure will also operate upon other organs, and affect them similarly—*e.g.*, kidneys, spleen, intestines.)

Course of the Disease.—The central intra-lobular vein becomes much distended and thickened, and the capillaries opening into it dilated and tortuous. The liver cells atrophy from the centre of the lobule outwards. The central zone of the lobule becomes pigmented (the pigment being derived either from the blood or bile), while at its periphery the cells tend to undergo fatty degeneration, so that on section there is seen a dark inner zone alternating with a pale peripheral one. Hence the liver presents a marbled, or 'nutmeg,' appearance.

Sooner or later some fibrosis occurs, first in the centre and then at the periphery of the lobules.

In advanced cases the cells of the inner zone are completely destroyed.

In the early stages the liver is enlarged as the result of the mechanical congestion; later on it becomes smaller from atrophy of the liver cells.

On section much blood may gush out, which when washed away leaves the characteristic 'nutmeg' appearance.

Lardaceous, or Waxy, Liver.

The organ is much enlarged—even to three times its normal size—and though its general contour is preserved, the edges become thick and rounded, and the whole mass is so compact that it cuts like raw bacon. The cut surface has a waxy appearance: hence the name.

A weak solution of iodine renders the amyloid material mahogany-brown, while gentian violet stains it a deep rose-pink and the normal tissues blue.

The change begins in the intermediate zone.

Abscess of the Liver.

Abscess of the Liver is always due to infection by micro-organisms. The two principal types are the *Pyæmic* and the *Tropical*.

Pyæmic Abscesses.—In ordinary pyæmia abscesses rarely occur in the liver, the more usual sites being the lungs and the joints. When pyæmic abscesses do involve the liver they are small and multiple, and contain a putrid, foul-smelling, yellow pus.

In *suppurative pylephlebitis* (*'portal pyæmia'*) the infection comes from some part drained by the portal system of veins, generally from ulceration of a portion of the alimentary tube; the abscesses may also follow operations for hæmorrhoids. They are small and numerous, and lie in the course of the distribution of the portal vein, the branches of which are seen to be filled with puriform clots.

Tropical Abscess.—This disease is in 90 per cent. of the cases associated with amœbic dysentery. The pus is of a slimy, gummy consistence, of chocolate colour, and composed of necrosed and liquefied liver cells with an admixture of blood, ordinary pus cells being either few or absent. *It is sterile*, no cultures of bacteria being obtainable by the ordinary methods. As pointed out by Manson, the amœbæ are numerous in the spreading margin of the abscess, and though absent in the pus when first drawn off, they make their appearance in the discharge about three days later—that is, when the walls of the abscess begin to granulate and contract.

The abscess is generally situated in the right lobe, and may contain several pints of fluid. After a time the pus tends to make its way to the surface of the liver, causing there adhesions to neighbouring structures, and, if the condition is untreated, the pus ultimately escapes into the pleura, lung, peritoneum, or through the abdominal walls, and in rarer cases into the stomach, gall-bladder,

hepatic duct, portal vein, inferior vena cava, pelvis of right kidney, pericardium, or even other parts.

Occasionally the abscess becomes surrounded by a thick fibrous capsule.

Cirrhosis of the Liver.

Of this disease there are three classical forms. The cause in each would appear to be some irritant, probably toxic in nature, present in the liver, and brought there—

(i.) *By the portal blood* (alcoholic cirrhosis);
(ii.) *By the bile-ducts* (hypertrophic cirrhosis); or
(iii.) *By the general circulation* (syphilitic cirrhosis).

Alcoholic Cirrhosis ('Hobnail Liver,' 'Gin-drinker's Liver,' Chronic Interstitial Hepatitis, Atrophic Cirrhosis).—The essential pathological change in this disease is an increase in the connective tissue *around the interlobular branches of the portal vein.* An irritant, circulating in the portal blood, first starts a *periphlebitis;* there then occurs a small-round-celled infiltration which ultimately becomes organized into fibrous tissue. This tissue tends to surround groups of several lobules rather than to envelop each individual lobule. In course of time the new tissue contracts and strangles the branches of the portal vein within the liver, and as a consequence there is great distension of the portal radicles in the gastro-intestinal tract and mesentery; hence ensue hæmatemesis, melæna, ascites, and enlarged spleen.

The irritant which provokes the cirrhosis is either the alcohol itself, impurities in the alcohol, or certain toxins liberated in the alimentary canal as the result of chronic catarrh caused by alcoholic excess.

'When we consider that cirrhosis is found in horses in Switzerland and in cattle in Nova Scotia; that it is common among abstaining Hindoos, who live on highly spiced foods; and that it attacks the Fuegians, who develop a severe form of it, and whose staple diet consists of large quantities of mussels, good and bad, with their abundant nitrogenous elements, it will be seen that the only factor common to all is the gastro-enteric tract, with its liability to irritation and putrefactive change' (Stenhouse and Ferguson).

The cirrhotic liver varies considerably in size, according to the stage the disease has reached. The organ is

always enlarged at first, sometimes to more than twice its normal size; on the other hand, it may be subsequently reduced to less than half its normal size. At the time of death in about 50 per cent. of cases it is enlarged, and in the other 50 per cent. contracted.

As seen in the post-mortem room, the typical cirrhotic liver presents the following appearances: Its surface is irregular, being marked by elevations which suggest the hobnails of a boot ('hobnailed' liver) and often by large round bosses as well. The capsule is usually thickened, and adherent to the surrounding peritoneum. On section the organ shows bands of fibrous tissue, which form a network throughout the liver substance, dividing it into 'islands' of various sizes, each of which contains separate groups of lobules; hence the name of 'polylobular' cirrhosis. The fibrous bands from the interior can be traced to the peritoneal surface, where they are seen to pass to the depressions between the 'hobnails.' The 'hobnails,' in fact, are portions of liver substance which have been thrust outwards by the contraction of these fibrous bands.

The new tissue consists of round cells, delicate spindle-cells (fibroblasts), and wavy bundles of fibrous tissue, the relative proportions of which vary with the duration of the process.

In the fibrous bands are numbers of new-formed blood-vessels, which anastomose with the branches of the hepatic artery; in some cases double rows of cubical cells are seen, suggesting a new formation of bile-ducts, but the significance of these is still doubtful. The liver cells undergo atrophy, and in beer-drinkers fatty degeneration of the peripheral zone of the lobule is common: when the atrophy of the cells is advanced, toxic symptoms supervene, not unlike those which occur in acute yellow atrophy.

The collateral vessels between the portal and systemic veins become dilated, and thus relieves the congestion of the portal area. This compensatory anastomosis is carried out principally between the following sets of veins: The œsophageal and gastric; the epigastric and internal mammary; the inferior mesenteric and hæmorrhoidal branches of the internal iliac; the portal branches in the round ligament of the liver, and the epigastric and internal mammary at the umbilicus (caput Medusæ);

branches of the portal vein in the mesentery, with the inferior vena cava and its branches (veins of Retzius).

Hypertrophic or Biliary Cirrhosis (Hanot's Disease).—In this comparatively rare disease the liver is greatly enlarged, firm, and smooth. The newly-formed connective tissue is more delicate than in the other kinds of cirrhosis, and it *surrounds each individual lobule;* hence the name of 'unilobular' cirrhosis applied by Charcot.

In the new tissue are enormous numbers of so-called bile-capillaries. As there is no obstruction to the portal circulation, hæmatemesis, melæna, and ascites are not present unless there is an associated portal cirrhosis.

The cause is unknown. The theory has been advanced that it is due to a microbic infection of the bile-ducts from the duodenum.

Obstructive Biliary Cirrhosis.—In certain cases of biliary obstruction, such as those due to impacted calculus, cancer of the liver or pancreas, an inter-lobular cirrhosis is met with, associated with dilated bile ducts and the formation of what look like bile-capillaries, but which probably consist simply of double columns of altered liver cells.

Syphilitic Cirrhosis—*Congenital Syphilis.*—In infants dying three or four months after birth it is not uncommon to find an interlobular cirrhosis uniformly affecting the whole liver. In many cases the new tissue *penetrates into the lobule, and so becomes peri-cellular.* The liver cells are degenerated.

Acquired Syphilis.—In this disease the liver may become infiltrated with a *diffuse gummatous material*, which by organizing causes it to be seamed with fibrous bands.

Definite Gummata may also occur, but these are always connected with a preceding syphilitic cirrhosis. The gummata form pale yellow, localized, well-defined, rounded masses, generally springing from the surface, which is often adherent to the neighbouring structures. They are surrounded by a fibrous capsule, and may be soft and pulpy, or hard like cartilage, according to their age.

Banti's Disease.

In this rare disease there is the combination of hepatic cirrhosis with splenic anæmia.

Cysts not infrequent. May be multiple.

Tumours of the Liver.

Cavernous Angeioma is the commonest of the non-malignant tumours of the liver. It may range in size from a pea to an orange.

Adenomata, which are very rare, occur in the form of nodules composed of acini lined with cubical épithelium.

Primary Sarcomata are also very rare. Secondary sarcomata sometimes form in the liver, particularly the melanotic variety.

Primary Carcinoma is rare, constituting only about 4 per cent. of hepatic cancers.

Secondary Carcinoma is common; indeed, it is the only hepatic tumour which is at all common. The primary growth may be situated in any part of the body, but its usual seats are the gastro-intestinal tract, the head of the pancreas, the gall-bladder, and the uterus. The hepatic tumours are usually multiple, and, owing, it is assumed, to the abundant blood-supply of the liver, grow quickly, the duration of life being seldom more than twelve months after the disease has been diagnosed. The heaviest livers on record have been cancerous.

Acute Yellow Atrophy.

This is a very rare disease (not more than 300 cases on record), probably toxic in nature, due to the action of a *hepato-lysin—i.e.*, a substance capable of dissolving the liver cells (see p. 162). It is characterized by so rapid an atrophy of the organ that in the course of a few days it may be reduced to half its original bulk. The malady is commonest in women, usually occurring in connection with pregnancy.

As seen after death, the liver is much shrunken. No longer preserving its normal shape, it flattens out when placed upon the table, lying loose in its capsule, which is wrinkled and can be pinched up between the fingers like a half-filled bag. On section the surface presents a yellow colour, the outlines of the lobules are indistinct, and the liver cells are for the most part broken down and replaced by a granular debris, though here and there are to be seen clumps of comparatively healthy cells.

1. Enlarged. Yellow. Fatty degen?. 2. Smaller Flabby Flat & wrinkled Leucin Tyrosine.

The disease bears a close resemblance to phosphorus-poisoning. As Vivian Poore pointed out, it is found in young pregnant prostitutes who have committed suicide by phosphorus-poisoning, and according to him many alleged cases have been in reality cases of phosphorus-poisoning.

Gall-Stones (Cholelithiasis).

Gall-stones are concretions consisting chiefly of cholesterin, with an admixture of bile-salts and bile-pigment. Most frequently they are found in the gall-bladder and intra-hepatic ducts. The gall-stones vary in size from small grains of sand to masses as large as a walnut. They are often multiple, the gall-bladder sometimes containing even hundreds. If multiple, they often present smooth, flat facets from mutual friction. When dry, the calculi float in water. They are most common in women over forty.

The first stage in the production of gall-stones would appear to be an antecedent catarrh of the gall-bladder or bile-ducts, due to microbic infection. As the result of such catarrh the epithelium becomes shed and forms a nucleus round which the hard matter is deposited. In other cases the bacteria themselves may form the nucleus.

Complications:

Obstructive jaundice.
Empyema of the gall-bladder.
Ulceration into duodenum.
Ulceration into hepatic flexure of colon.
Carcinoma of gall-bladder.
Stenosis of the common duct.
Cirrhotic changes in liver and pancreas.

DISEASES OF THE PANCREAS.

Pancreatitis may be acute or chronic. Of the acute form there are three chief varieties:

Acute Hæmorrhagic Pancreatitis.—In this disease the greater portion, if not the whole, of the gland becomes infiltrated with blood and its cells necrosed. There may also be fat necrosis in the pancreas, omentum, and elsewhere.

Suppurative Pancreatitis is characterized by the presence of either a single abscess or of small multiple ones.

Gangrenous Pancreatitis may affect a part or the whole of the gland, the tissue being converted into a dark slate-coloured mass.

According to Mayo Robson, impaction of gall-stones in the common duct is the most frequent cause of acute pancreatitis. Other causes are infection from the duodenum and infection from the blood. Most probably in all cases the essential factor is some virulent toxin, which, entering the substance of the gland, excites acute inflammation there.

In **Chronic Pancreatitis** there is an overgrowth of the fibrous tissue of the organ, with atrophy of the glandular elements. In extreme cases the condition is known as *cirrhosis of the pancreas*.

Pancreatic Cysts may be of several kinds: *Retention cysts*, which result from obstruction to the outflow of the pancreatic secretion—*e.g.*, from impacted calculus or pressure from without, as from chronic pancreatitis; *cysts in connection with growths, e.g.*, adenoma, carcinoma; *hæmorrhagic cysts; hydatid cysts.*

Tumours of the Pancreas.

Adenomata may occur, but they are extremely rare.

Primary Carcinoma usually affects the head of the pancreas. It also is rare.

Pancreatic Calculi are sometimes met with. They consist principally of calcium carbonate, and they may cause obstruction in any part of the main pancreatic duct. They are usually multiple.

Pigmentary Cirrhosis of Hæmochromatosis (Bronzed Diabetes) is a condition characterized by pigmentation of the secreting cells of the liver and pancreas, fibrosis of these organs, pigmentation in the skin, and finally diabetes. The explanation given of these phenomena is as follows: As the result of a toxin in the system, the blood cells are destroyed in considerable numbers, and hæmosiderin is deposited in the liver and pancreas. Hypertrophic cirrhosis of the liver and chronic interstitial pancreatitis develop, in consequence of the irritation caused by this pigment. In course of time the parenchyma of the pancreas, being compressed by the new tissue, atrophies, when glycosuria supervenes.

DIABETES MELLITUS.

Diabetes is a clinical term, and is used in a generic sense like jaundice, to indicate a symptom—*i.e.*, persistent glycosuria.

The sugar which appears in the urine is *dextrose* ($C_6H_{12}O_6$).

(Normal urine contains dextrose, but in insufficient quantity to give the ordinary reaction with Fehling's solution.)

Experimentally, diabetes can be induced in animals by any of the following methods :

1. Puncturing the floor of the fourth ventricle.
2. Removing the pancreas.
3. Administering phloridzin.
4. Administering adrenalin.

1. *Puncturing the Floor of the Fourth Ventricle.*—The explanation of the induction of diabetes by this method probably is that the puncture damages a centre in the medulla which controls the glycogenic action of the liver cells.

'There are experiments recorded which show that the liver nerves have a direct influence on the liver cells, quite apart from their influence on the bloodvessels' (Halliburton).

2. *Removing the Pancreas.*—Removal of the entire pancreas in animals causes severe and fatal glycosuria; if, however, even a very small portion of the gland is left behind, glycosuria does not ensue. The glycosuria thus induced has been ascribed to the loss of the internal pancreatic secretion, which is assumed to influence the carbohydrate metabolism of the tissues.

'The "islets of Langerhans" have probably nothing specifically to do with the production of this internal secretion, for it has recently been shown that the islets are only phases in the life-history of the ordinary secreting acini' (Halliburton).

3. *Administering Phloridzin.*—By the administration of this glucoside a very severe form of diabetes is induced, characterized by abundant sugar in the urine, though the blood contains no more than the normal quantity; it is *glycosuria without glycæmia*, the sugar being formed in the kidney by some substance brought to it by the blood.

'If the phloridzin is directly injected into one renal artery, sugar rapidly appears in the secretion of that kidney, and, later, in that of the other kidney' (Halliburton).

4. *Administering Adrenalin.*—In the diabetes induced by the administration of adrenalin there is both *glycæmia and glycosuria*.

Pathological.—As regards the causal pathology of

clinical diabetes, the only fact definitely known is that in a certain proportion of cases the pancreas, post-mortem, is found to be diseased. Probably, however, it is only the severer forms of diabetes—*i.e.*, those associated with rapid wasting, great thirst, and abundant glycosuria—which can be ascribed to disease of this organ.

In these cases the pathological changes found in the pancreas consist of an *increase of the connective-tissue stroma* (*fibrosis*), *accompanied by atrophy of the parenchyma*.

Glycosuria is uncommon in carcinoma of the pancreas, the reason being that the growth rarely destroys the entire gland.

Diabetic Coma.—The occurrence of this symptom is probably due to the presence in the blood of the fatty acid, *β-hydroxybutyric acid*, which originates from the fat in the body. Both acetone and accto-acetic acid (derivatives of β-hydroxybutyric acid) are usually present in the urine of patients in whom diabetic coma is impending, but that they are not the actual cause of the coma is proved by the fact that when they are artificially introduced into the blood no narcosis results.

'The β-hydroxybutyric acid formed in diabetes is, by oxidation, partly converted into aceto-acetic acid, and, in the urine, this loses carbonic dioxide, and so is partly converted into acetone' (Halliburton).

β-hydroxybutyric acid is probably a normal product of fat metabolism, but whereas in health it is oxidized into carbonic acid and water, in diabetes this oxidation is not effected.

Diabetic Gangrene is a complication generally found only in elderly diabetics (about the age of sixty), and it is often the first indication of the existence of diabetes. Its exciting cause is commonly a slight injury, such as may result from wearing tight boots, or from pressure on a corn. Its most frequent site is the foot. There are two chief types—

(*a*) Mummification.
(*b*) Perforating ulcer.

(*a*) *Mummification*.—The toes become cold and discoloured, and in course of time mummified. They may

now be cast off, the parts healing up, or the gangrene may extend to the dorsum of the foot.

(*b*) *Perforating Ulcer.*—Here the disease usually starts in the ball of the great toe, often around a corn. The corn, by suppurating, causes the formation of a painless ulcer, having steep edges, bordered by heaped up and thickened epidermis, a condition very similar to that found in certain cases of tabes dorsalis. A dusky purple areola soon surrounds the ulcer, which in time becomes gangrenous; and in this manner the gangrene slowly spreads along the foot until it may even extend as far as the calf of the leg. Whilst confined to the foot it usually remains 'dry,' but once it invades the soft tissues of the calf it tends to become 'moist,' and may at any time be complicated by septic infection.

In all cases of diabetic gangrene the arteries supplying the part are diseased, the endothelium being greatly thickened and the arterial channels reduced in size, or even obliterated.

Is diabetes a germ disease? Sir Patrick Manson said that in China diabetes was rare, although the Chinese were rice-eaters and were frequently overfed and overworked, and therefore subject to most of the conditions which had been stated to be provocative of the disease. The endemicity of diabetes in Bengal was interesting. It might be, however, that diabetes, which had been for so long attributed to food, exposure, nervous influences, heredity, and so forth, might, like other ailments with similar history, come to be proved to be due to a specific organism. Leprosy, tuberculosis, sleeping sickness, and several other diseases which occurred to one, had each in turn been ascribed to general causes, whereas they now know that a specific organism was found to be the etiological agent in each. The diabetes of Bengal would seem also to be probably one of the germ diseases (British Medical Association, August, 1907).

DISEASES OF VEINS.

Varix (Varicose Vein).

Varix consists of a stretching of the venous wall, both laterally and longitudinally, in consequence of which the vein becomes dilated and elongated—it may even become

as large as the wrist and three times as long as normal. In consequence of the elongation the vessel is tortuous. The walls undergo a compensatory thickening, and when cut crosswise the vessel gapes like a divided artery. It is probable that the essential cause of varix, when it occurs idiopathically, is a defect in the muscular coat, which normally, by its tonic contraction, resists the action of a stretching force more effectually than any passive tissue can. Either we must suppose that there is a congenital defect of the muscular coat in such cases, or that its muscle fibres remain unduly relaxed, and so undergo atrophy. In any case the most notable change observed in the wall of the varicose vein is the replacement of its normal elements by fibrous tissue. Here and there the wall is thinned and dilated into pouches, over which the skin may become adherent. The valves share in the process and undergo cicatricial contraction, ultimately shrinking considerably, and even disappearing, and in consequence of the dilatation of the vessel and the incompetence of its valves, the varicose vein has to support a longer column of blood, which throws an extra strain on its walls. In course of time there may be no competent valves between the affected vein and the right heart, and this explains *the 'impulse' on coughing.*

Complications:

Pigmentation of overlying skin.
Thrombosis.
Phlebitis.
Adhesion to skin.
Ulceration (varicose ulcer).
Eczema.
Œdema of the ankle.

A dilated pouch adherent to the skin may give way by ulceration, or even by bursting without previous ulceration. Dangerous bleeding then ensues, which may prove fatal in a few minutes. This bleeding takes place in a different way from ordinary hæmorrhage, for, the dilated vein being rigid and not collapsing, and the valves being incompetent, the blood comes *chiefly from the cardiac side* of the perforated vessel—it is a reflux.

Occasionally calcareous plates are met with in the thickened walls of a varicose vein, and in rare cases *phleboliths* may develop in the interior.

The veins commonly affected by varix are the internal and external saphenous, the pampiniform plexus of the spermatic cord, and the hæmorrhoidal.

Sometimes a varicose vein is not much lengthened—*e.g.*, the internal saphenous vein may stand out as a more or less straight dilated tube from the ankle to the groin. In such cases we must assume that the longitudinal muscle fibres are normally functional.

Phlebitis is inflammation of the venous wall, and is always associated with thrombosis.

There are two classical forms of phlebitis—(*a*) the infective or suppurative, and (*b*) the simple or non-suppurative.

(*a*) In *Infective Phlebitis* the venous wall becomes inoculated with pyogenic organisms, and a clot soon forms inside the vessel. The cause may be a septic wound, extension of inflammation from some neighbouring septic focus, such as acute infective osteomyelitis, middle-ear disease, or facial carbuncle, or the infecting material may be carried by the general blood-stream.

The venous wall, the surrounding tissues, and the thrombus inside the vein, are crowded with septic microorganisms. The clot breaks down, and septic emboli may be discharged into the blood-stream, and so lead to pyæmia, unless a ligature be placed between the disintegrating clot and the heart. In favourable cases infection of the blood-stream is prevented by the portion of the clot at the distal end remaining firm instead of disintegrating.

(*b*) *Simple Phlebitis* is always associated with thrombosis. The thrombosis may cause the phlebitis, or the phlebitis may cause the thrombosis, but the two pathological conditions always coexist.

The causes are injury, extension of surrounding inflammation, and certain blood states—the 'gouty phlebitis' of Paget, for example, and thrombosis (see Thrombosis). Varicose veins are much more liable to inflammation than healthy ones.

The coats of an inflamed vein are infiltrated with small round cells, the endothelium is swollen and may become detached, and the surrounding tissues are œdematous. A clot forms in the damaged part of the vein, and becomes adherent to it.

Terminations:

Resolution.
Organization.
Tunnelling—*i.e.*, the axial part of the thrombus is absorbed, and the peripheral part organizes.
Embolism.
Suppuration.
Phleboliths.

DISEASES OF ARTERIES.

Acute inflammation of an artery may be the result of trauma, infection from septic wounds, or irritation by emboli. Excluding these, the classical forms of arteritis are:

Acute endarteritis—Acute aortitis.

Chronic endarteritis:
- Atheroma, or endarteritis deformans:
  - Secondary calcification.
  - Atheromatous abscess.
  - Atheromatous ulcer.
- Primary calcification.
- Endarteritis syphilitica.
- Endarteritis obliterans.
- Endarteritis tuberculosa.

Acute Endarteritis.—The best example of this rare disease is *acute aortitis*, which is usually the result of infection from the aortic valves in malignant endocarditis. In other cases it results from blood infection. Its usual situation is at the beginning of the aorta and round the origin of its branches.

The process commences as a small-round-celled infiltration of the inner coat, producing sharply defined, raised, gelatinous patches, circular or ovoid in outline, and soft and elastic in consistence. The infiltration may extend into the middle and outer coats, in which case the new elements may organize into fibrous tissue. The endothelium, as a rule, remains intact.

The disease may lead to aneurism, or pass into endarteritis deformans.

Atheroma and Endarteritis Deformans are described by different authors in different ways. In the following account the two terms are used as meaning the same thing.

Atheroma is common in men over forty with high blood-pressure, especially in connection with granular kidney. The connection between atheroma and high blood-pressure is further shown by the fact that the former

is seldom, if ever, met with in the pulmonary circuit, except when, from disease of the left heart, the blood-pressure in that circuit has been chronically augmented. Again, atheroma never occurs in the systemic veins except as the result of a long-sustained augmentation of venous pressure.

The disease occurs in those arteries which are exposed to the greatest strain, as in the arch of the aorta and at the points at which large branches are given off, or where a trunk bifurcates, the most frequent sites being—

The aortic arch.
Round the orifice of its large branches.
The coronary arteries.
Round the orifice of the cœliac axis.
At the bifurcation into the iliacs.
The cerebral arteries.
The renal arteries and their branches.

As it affects the Aorta and Large Vessels.—Small round cells, in the form of scattered foci, infiltrate the *intima*, replacing the normal elements of the part. In course of time these foci coalesce to form pale yellowish, semi-gelatinous patches, slightly elevated above the surface. The further progress may be in one of two directions: the patches may (*a*) calcify, or they may (*b*) soften and break down.

(*a*) In the former case fatty degeneration of the cells takes place; the contents afterwards dry up, and lime-salts and cholesterin are deposited in the shrivelled mass, which is thus ultimately converted into a hard calcareous plate. This is known as *secondary* or *laminar calcification*, so called to distinguish it from the primary annular calcification found in the middle coat of such arteries as the tibials (see p. 99). At this stage the interior of the vessel is seen to be studded with hard, milky, circumscribed, non-vascular patches. On careful inspection, the endothelium is generally found to be intact, however advanced the process.

(*b*) On the other hand, the contents of the patches, instead of drying up, may liquefy and form an *atheromatous abscess*, which, upon the endothelium giving way, may become converted into an *atheromatous ulcer*.

Should this latter develop, a small coagulum will form over the roughened part.

Cellular infiltration into the middle coat also takes place, while the outer coat may be the seat of a varying amount of compensatory fibroid thickening.

So long as the intima alone is affected, the vessel wall is not likely to yield before the pressure of the blood, but directly the muscle fibres, which by their active contraction offer an effective resistance to that pressure, are implicated, the damaged part of the vessel is liable to yield slowly and thus lead to the formation of an aneurism.

As it affects the Smaller Vessels (*Coronary, Cerebral, Renal, etc.*).—The process here is essentially the same as in the case of the large vessels. The patches, however, are often in the form of nodes, sometimes suggesting in appearance a 'signet-ring,' which may project so far into the lumen as partially to occlude it.

Primary Calcification affects the medium-sized arteries —*e.g.*, those below the elbow and knee. The process begins in *the middle coat*, the muscle fibres of which become infiltrated with lime-salts, and as these fibres run circularly round the vessel, the calcification takes the form of a succession of rings, recalling the appearance of ipecacuanha. Ultimately the artery may be converted into a rigid tube. In the case of the tibials the intima may become detached; thrombosis is then liable to occur, and, as a result of this, gangrene (see Senile Gangrene).

Corresponding vessels on opposite sides of the body are usually involved, *symmetry being a marked feature of the disease.*

Endarteritis Syphilitica consists of a diffuse gummatous infiltration of the intima, extending all round the circumference of the vessel wall. The intima in consequence is greatly thickened and, by encroaching on the lumen, narrows the blood channel until this may be converted into a mere slit, thus favouring the formation of a thrombus. Capillaries are developed in the new tissue, but only to be obliterated as organization into fibrous tissue takes place. Neither fatty nor calcareous degeneration occurs. Syphilitic endarteritis is often associated with a peri-arteritis.

The disease is most common in the *arteries at the base of the brain and in the arteries of gummata* (see Gummata). In the former case the new tissue is apt to occur in the form of nodules, which often lead to thrombotic occlusion (syphilitic thrombosis). This is the most frequent cause of hemiplegia in adults (especially men) under forty years of age.

Endarteritis Obliterans is probably an advanced stage of endarteritis syphilitica. There is great subendothelial proliferation, the change involving also the middle and external coats. New capillaries are formed, and the final result is the formation of fibrous tissue, which narrows the lumen and may ultimately occlude it. In some cases occlusion is brought about by thrombosis.

Endarteritis Tuberculosa generally involves the perivascular lymphatic sheaths, but tubercles may also develop *in* the arterial walls themselves. Under these circumstances the intima becomes greatly thickened, and the lumen reduced in size and even obliterated.

Arterio-Fibrosis.

Apart from the diseases just dealt with, there is a condition of the arteries associated with advancing years which is commonly known as *arterio-fibrosis*.

Old age is a relative term, and, medically considered, is to a large extent determined by the condition of the arteries—*i.e.*, whether they are soft and elastic or hard and rigid.

After a certain period of life the arteries, in common with the other tissues, tend to harden. This results from a general fibrosis, which impairs the normal elasticity of the vessel walls and makes them rigid. The test of a healthy artery is that if such a vessel as the radial or temporal be pressed by the finger it melts away into, and can scarcely be differentiated from, the surrounding tissues, whereas a thickened vessel can be rolled beneath the finger. There is no precise age at which the senile change comes on. Sometimes the arterio-fibrosis sets in early. A man of thirty, for instance, may have the arteries natural to a man at sixty, and *vice versa*. Hence the aphorism, *A man is as old as his arteries*. Thomas Parr is said to have had arteries which at the time of death showed nothing abnormal (Gibson, 'Diseases of the Heart').

Early arterial degeneration runs in families. Renal disease, diet, alcohol, toxæmias, heredity, and other influences, all play their part in the production of premature arterio-fibrosis.

Aneurism.

An aneurism (*aneurisma*, a dilatation) is a cavity which contains blood, either fluid or coagulated, and which communicates with an artery. The walls of the cavity are formed either of the expanded portion of the vessel wall or of the tissues around.

It is during the middle period of life, between the ages of thirty and fifty, that aneurism is most frequently met with.

In children aneurism is probably always due to embolic arteritis.

'Dissecting' aneurism is more common in women than in men; 'carotid' aneurism is equally common in the two sexes, while other kinds are thirteen times more common in men than in women.

Classification.

1. Spontaneous	Fusiform.
	Sacculated.
	Dissecting.
2. Traumatic	Circumscribed.
	Diffuse.
3. Arterio-venous	Aneurismal varix.
	Varicose aneurism.

A **Spontaneous Aneurism** is one that develops in consequence of pre-existing disease of an artery.

A **fusiform aneurism** is one in which there is dilatation of the entire circumference of the artery, the result of an *extensive disease of its walls*. The usual seat is the arch of the aorta. As a rule, the vessel is involved for a considerable portion of its length. In addition to the dilatation there is *elongation*, which may be considerable. Thus, the arch of the aorta may be increased in length by some inches. From the main dilatation small 'saccular' aneurisms may spring.

On examining the structure of a fusiform aneurism, it will be found that the internal coat shows widespread atheromatous changes: it is stiff and rough, calcareous plates are frequently scattered over the internal surface, and in places where the endothelium is injured shreds of fibrin are adherent. The middle coat is atrophied in proportion to the degree of dilatation. The outer coat is compensatorily thickened and strengthened by the

formation of new fibrous tissue. It is owing to this thickening that the course of an uncomplicated fusiform aneurism is usually chronic—either remaining stationary or increasing very slowly, and thus continuing for many years without causing death.

A **sacculated aneurism** is one in which the dilatation involves only a part of the circumference of the artery, the result of a *localized* disease of its walls. When the aneurism is of very small size, the three arterial coats are spread out over it; when somewhat larger, the internal coat atrophies and disappears; when it attains a still larger size, the middle coat also atrophies and disappears, and the sac of the aneurism is now constituted by the external coat strengthened by a thickening of the surrounding areolar tissues. Usually the interior of a sacculated aneurism contains fibrin arranged in concentric, overlapping layers, no single layer reaching over the whole sac. The older layers on the outside are of a pale buff colour, those towards the interior being darker.

Organization of the fibrin is rare, because of the forcible stream of blood through the artery and aneurismal sac. *No organization can take place in the aneurism unless the artery from which it springs is occluded.* Occlusion may occur either by extension of the clot from the sac into the artery, by a detached piece of clot plugging the artery, or in consequence of surgical compression or ligature.

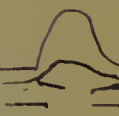
Complete arrest of the circulation leads to the formation of an ordinary, soft blood-clot (*clot en masse*); this is very rare, however, and is only possible when the mouth of the aneurism, or the main trunk of the artery immediately beyond it, becomes plugged by a detached piece of clot.

Causes of Death from Aneurism.—The tendency of aneurisms is to *rupture*, either into the pericardium, pleura, trachea, œsophagus, peritoneum, or externally. *Embolism* of the cerebral arteries may occur in consequence of the detachment of a portion of the clot into the blood-stream. Death may also result from *pressure* on vital parts.

Ætiology of Spontaneous Aneurism.—It can be definitely stated that the essential cause of 'fusiform' aneurism is a preceding widespread atheromatous change in the artery (especially such as destroys the middle coat), for evidence of this is always present

in the interior of the dilatation. In a 'sacculated' aneurism, however, the case is different, for owing to the small area from which the aneurism springs, coupled with the further fact that but little of the arterial coats remains in the sac, the exact nature of the local disease which starts the process is a difficult matter to determine. Syphilis, atheroma, and alcohol affecting the media, in conjunction with the strain of heavy muscular exertion, would appear to be the most probable factors in the causation. To put it briefly, those who worship at the shrines of Venus, Vulcan, and Bacchus are the most liable to spontaneous aneurisms.

An important function of the muscular coat of arteries and veins, practically the sole function in the large arteries and veins, is by its *active contraction* to prevent dilatation. *Passive* tissue must perforce yield to long-continued pressure. We should therefore expect the essential cause of aneurism to be a weakening of the muscular coat.



A **Dissecting Aneurism** is one in which there is a longitudinal rupture of the internal coat, the blood being forced between the layers of the middle coat. It is generally the result of the bursting of an atheromatous abscess. The blood may escape by an aperture in the outer coat and become diffused externally, or it may open again into the lumen of the artery through another atheromatous spot. It is most common in the aorta, and occurs more frequently in women than men.

A **Traumatic Aneurism** is a cavity containing blood, either fluid or coagulated, communicating with an artery, and produced by an injury dividing all the coats.

If the blood escapes slowly, compression of the tissues around leads to the formation of an adventitious sac, and the result is a *circumscribed traumatic aneurism*. On the other hand, if the blood escapes quickly and in abundance, it finds its way along the connective-tissue planes, travelling in the direction of least resistance, and the distending force being too great to allow of the formation of a sac, a *diffuse traumatic aneurism* results.

Miliary Aneurisms are about the size of a small pin's head, and are met with in the cerebral arteries, more especially those coming off from the circle of Willis—*i.e.*, the *central* as distinguished from the *cortical* arteries. It is from rupture of such a miliary aneurism that 'spontaneous' cerebral hæmorrhage is practically always due. When this occurs in a child, it is generally from an aneurism which has developed secondarily to embolism.

The pathology of miliary aneurisms is still somewhat doubtful. Charcot taught that they do not occur secondarily to atheroma; that, whereas this condition starts in the intima and spreads outwards, the arterial change which leads up to miliary aneurism begins in the external coat of the artery and spreads inwards. Certain it is that atheroma of the cerebral vessels may be extensive and miliary aneurisms conspicuous by their absence from them, *and vice versa*. One clinical fact stands out prominently in connection with miliary aneurisms: they never occur in association with low blood-pressure. Hence the low blood-pressure individual does not die from cerebral hæmorrhage.

Miliary aneurisms, when not rupturing, tend in process of time to become occluded, from thrombosis of their contained blood and subsequent shrinkage.

An **Arterio-Venous Aneurism** is the result of communication between an artery and a vein lying in juxtaposition. It is generally of traumatic origin—*e.g.*, when the brachial artery and the median-basilic vein at the bend of the elbow are wounded simultaneously. If the two vessels are in close contact and become adherent, the blood passes directly from the high blood-pressure artery into the low blood-pressure vein, and the latter will become dilated into a pulsating, fusiform or globular pouch with thickened walls, the dilatation extending also into the vein-tributaries, which become varicose and tortuous. This is known as *aneurismal varix*.

Instead of the blood passing directly from the artery into the vein, it may well out between the two tubes, and become enclosed in an adventitious sac communicating with both. This condition is known as *varicose aneurism*.

SHOCK.

The terms 'shock,' 'syncope,' and 'fainting' all mean practically the same thing. The pathology of shock concerns essentially the cardio-vascular system. There is—

(*a*) *Paralysis of the vaso-motor centres*, particularly of those controlling the splanchnic area—this allowing the blood to accumulate in the portal system of veins ('bleeding into one's own veins').

(*b*) *Enfeebled cardiac action*, because less blood flows into the heart, which in consequence loses the stimulus of the normal endocardial pressure.

The output of the heart being less than normal, the arteries are underfilled, and this explains the thready pulse (often irregular and intermitting), the cold and clammy skin, with fall in the surface temperature, and the anæmia of the brain which renders the patient partially unconscious.

The causes are—

(1) Mental, such as an emotion;

(2) Physical, such as the impulse ascending from a wound.

The degree of shock varies with—

(*a*) The nervous susceptibility of the patient; and

(*b*) The severity of the injury.

COLLAPSE.

The pathology of collapse consists essentially in the loss of fluid from the body.

Collapse accompanies such diseases as are attended by constant vomiting or diarrhœa, examples being the diarrhœa of young children, Asiatic cholera, the profuse and prolonged vomiting of strangulated hernia, intestinal obstruction, and acute generalized peritonitis. Owing to the abstraction of such large quantities of fluid, the blood becomes inspissated and resembles tar, the muscles, liver, spleen, and kidneys becoming tough and leathery.

Collapse may also result from severe hæmorrhage.

CHRONIC ALCOHOLISM.

The pathology of chronic alcoholism consists of:

An increase of the fibrous at the expense of the higher elements of the tissues. This is particularly marked in the liver, arteries, and nervous system.

A tendency to fatty degeneration, especially of the heart. At the coroners' inquests held in London the common cause of sudden death in drunkards is found to be fatty degeneration of the heart.

Catarrh of mucous membranes, alimentary and bronchial.

The above-mentioned changes may be caused either by the direct action of the alcohol on the tissues or by bacterial toxins developed in the catarrhal alimentary tract. Probably both factors co-operate.

'When the sot has descended through his chosen course of imbecility or dropsy to the dead-house, Morbid Anatomy is ready to receive him—knows him well. At the post-mortem she would say: "Liver hard and nodulated; brain dense and small, its coverings thick." And if you would listen to her unattractive but interesting tale, she would trace throughout the sot's body a series of changes which leave unaltered no part of him worth speaking of. She would tell you that the once delicate, filmy texture which, when he was young, had surrounded like a pure atmosphere every fibre and tube of his mechanism, making him lithe and supple, has now become rather a dense fog than a pure atmosphere—dense stuff which, instead of lubricating, has closed in upon and crushed out of existence more and more of the fibres and tubes, especially in the brain and liver—whence the imbecility and the dropsy' (Moxon).

DISEASES OF DUCTLESS GLANDS.

Diseases of the Thyroid Gland.

The thyroid is a ductless gland, composed of acini lined with cubical epithelium, and filled with the so-called colloid material, which contains a proteid — *thyroiodine* — remarkable for the presence in it of iodine. The stroma is abundantly supplied both with bloodvessels and lymphatics. The gland is developed from the pharynx, and in fœtal life has a duct—the thyroglossal—which opens into the foramen cæcum of the tongue.

Pathological and experimental observations point to the fact that the thyroid gland elaborates a secretion which exerts an important influence on the development and nutrition of the whole body.

Goitre (Bronchocele).

Goitre is a clinical rather than a pathological term, and embraces all non-malignant enlargements of the thyroid gland.

Classification
- Parenchymatous
  - Cystic.
  - Fibrous.
- Adenomatous.
- Exophthalmic.

Parenchymatous Goitre consists of an overgrowth of the acini, and to some extent of the stroma. The acini may become cystic ('cystic' goitre), or the stroma may be abundant ('fibrous' goitre). It is usually bilateral.

Adenomatous Goitre is characterized by the formation of large acini, which are enclosed within a distinct capsule separating them from the rest of the gland—thus constituting a true adenoma. In some cases the acini are converted into *cysts* containing a thin brownish fluid. It is often unilateral.

Exophthalmic Goitre is characterized by three sets of changes:

(*a*) Alteration in the alveoli.
(*b*) Increase in the connective-tissue stroma.
(*c*) Dilatation of the bloodvessels.

(*a*) The cubical epithelial cells lining the acini become cylindrical. New acini are formed by diverticula from old ones.

(*b*) In the newly-formed connective tissue of the stroma nodules of lymphoid tissue are often found.

(*c*) The bloodvessels (more particularly the veins) become greatly distended and their walls friable, so that during an operation on the gland hæmorrhage is apt to be copious.

The most probable explanation of the symptoms of exophthalmic goitre is that they result from an excessive formation of the normal, or the formation of an abnormal, secretion, which increases the katabolism of the tissues, causing an increased output of carbonic acid and urea, together with loss of weight. Most of the characteristic symptoms—the sweating, the pigmentation of the skin, the tachycardia, the nervous agitation—are referable to this augmented katabolism.

The disease occurs eleven times more frequently in women than in men (Murray).

Malignant Tumours.

As the thyroid gland contains both mesoblastic and hypoblastic elements, *sarcomata* and *carcinomata* can occur, but they are extremely rare.

Cretinism and Myxœdema.

It is now recognized that both these diseases depend upon atrophy of the thyroid and diminution or entire absence of its secretion.

Cretinism is a physical and mental defect of development associated with a congenitally defective thyroid. The gland may be either smaller or larger than normal, but in all cases the acini are ill-developed.

The symptoms are rarely noticed until the child has reached the age of six months. The teeth erupt late, articulation and walking are long delayed, and by the time adult life is reached the cretin may be mentally and physically as undeveloped as a child of five.

The head in cretins is large and broad, the nose flat; the eyes are widely separated, the lips greatly thickened, as is also the tongue, which usually protrudes from the mouth. The skin is coarse and rough. The abdomen is pendulous, and there is often knock-knee. The hairs of the body are scanty.

Myxœdema was first described by Gull as 'a cretinoid state supervening in adult life in women.' In it the thyroid is always diseased, the acini being atrophied and the connective tissue hypertrophied. The symptoms are due either to auto-intoxication, the result of the accumulation in the blood of substances normally destroyed by the thyroid, or to absence of the secretion. The latter is the more probable.

The skin of the body generally becomes loose, flabby, and thickened. The alæ nasi, eyelids, and lips become swollen and puffy, as likewise the fingers and toes. These changes depend upon an increase in the connective and adipose tissues of the parts.

The organism tends towards an anabolic rather than a katabolic condition, the output of carbonic acid and urea being diminished while the weight increases.

As Halliburton points out, the mucin is not necessarily in excess in the tissues, for in only two out of ten cases of myxœdema examined by him did he find an excess. Hence the name by which the disease is generally known is not well chosen.

Implantation of a sheep's thyroid into the subcutaneous

tissues, or the administration of thyroid extract, may effect a striking improvement in the symptoms.

Cachexia Strumipriva is the condition which results from complete extirpation of the thyroid. The symptoms closely resemble those of myxœdema.

Suprarenal Capsules.

Oliver and Schäfer obtained from the medullary portion of the suprarenal capsules a substance—*adrenalin*—which has a special action in contracting the peripheral arterioles and causing a great rise in the arterial blood-pressure.

According to Abelous and Langlois, one of the functions of the suprarenals is to destroy the toxic products of muscular and mental exertion, for they found that if these organs are removed and the animal is made to perform muscular work, toxic symptoms soon develop.

Addison's Disease is characterized by great muscular weakness, low blood-pressure, rapid, feeble pulse, a tendency to syncope, vomiting, and pigmentation of the skin, which symptoms are always associated with disease of the suprarenal capsules. In the great majority of cases, if not all, the change consists in a *tubercular destruction* of the gland tissue.

New growths sometimes occur but they are rare, and it is very doubtful if they are ever the cause of genuine Addison's disease, inasmuch as they do not, like tubercle, destroy the suprarenals on both sides.

The Pituitary Body.

This structure is peculiar in being developed in part from the alimentary canal and in part from the brain.

Acromegaly is a disease characterized by hypertrophy of the *bones* of the face, hands, and feet. In the face, the lower jaw especially is affected, projecting in advanced cases beyond the upper. The soft part of the nose, the lobe of the ear, the lips and tongue, hands and feet, also become thickened, and the patient in many respects reverts to the simian type.

In all cases which have been examined after death the pituitary body has been found hypertrophied or the seat of a tumour. Probably the disease results from an excess of, or some alteration in, the secretion of this gland.

The acromegalous man takes on many of the features of the anthropoid ape, the former resembling the latter in the following among other particulars: In the possession of cranial crests, prominent supra-orbital ridges and malars, and massive jaws; in the prominence of the eyes, wrinkling of the lids, furrowing of the forehead, breadth and fleshiness of the nose, and thickness of the lips; in the shortness and thickness of the neck; in the backward convexity of the cervico-dorsal spine and consequent stoop; in the long sagittal diameter of the thorax and the abdominal character of the breathing; in the bowing of the legs and massiveness of the skeletal and muscular systems; in the existence of pads, separated by deep furrows, on the palms and soles, and in the longitudinal striation of the nails; in the coarseness and looseness of the skin and tendency to pigmentation, and in the coarseness and excessive growth of hair; in the depth of the voice; in the activity of the cutaneous glands and susceptibility to cold (H. Campbell).

The Thymus Gland.

This gland is developed from the pharynx, and when fully formed is chiefly composed of lymphoid tissue, the corpuscles of Hassal representing the original hypoblastic elements. The gland begins to atrophy after the second year of life, and by the age of puberty is converted into a small mass of fatty connective tissue. As regards its functions nothing is at present definitely known.

Status Lymphaticus is the condition sometimes met with in children and young adults, characterized by persistent and enlarged thymus, hypertrophied lymphatic glands, and increase in the lymphoid tissue of the tonsils, of Peyer's patches, and of the Malpighian bodies in the spleen. The condition has been found in a number of cases in which sudden death had occurred during the administration of anæsthetics, as well as in certain cases of death from trivial causes.

Other Hormonic Affections.

Premature Puberty.—Puberty may make its appearance as early as the second year, owing to the premature entrance into the blood of some hormone, or hormones (p. 26), which normally bring it about. In some of these cases there may be considerable muscular development and a large deposit of fat, and in such the adrenals are generally involved in disease.

Infantilism.—In this condition development does not proceed beyond the infantile stage. It is probably due to

the absence from the blood of some substance, or substances, necessary to normal development. One such substance appears to be provided by the pancreas, for cases in which diarrhœa has been a prominent symptom have been recorded (by Byrom Bramwell and others) which have been greatly improved by the administration of pancreatic extract.

Premature Senility.—This is due to the premature entrance into the blood of substances which promote senile changes in the tissues, or to the absence from the blood of substances which keep the tissues youthful.

Before the patient has reached the age of twenty, it may be, the skin becomes wrinkled, the hair blanched, the spine rigid, the arteries atheromatous, and the tissues generally exhibit other features characteristic of old age.

SYPHILIS.

According to the researches of Schaudinn and Hoffmann, syphilis is due to the presence of the *Spirochæta pallida* (*Treponema pallidum*), this organism having been found—

Acquired syphilis	in the primary sores. in the skin lesions. in the mucous membrane lesions. in the lymphatic glands. in the blood.
Congenital syphilis	in the skin lesions. in the liver. in the spleen. in the lymphatic glands. in the lungs. in the blood.

Metchnikoff and Roux have also discovered it in the syphilitic lesions of the higher apes inoculated with the virus taken from human beings.

Schaudinn has found the organism in all cases of syphilis up to the tertiary stage, but he has failed hitherto to find it in the latter. It has to be distinguished from the *Spirochæta refringens*—a common genital saprophyte.

The *Spirochæta pallida* is supposed to be *a protozoon*, and, as described by Schaudinn, is a long thread-like organism, from

4 μ to 14 μ in length and 0·25 μ in breadth, tapering at both ends, with eight to sixteen corkscrew-like spirals, which are visible in the living animal, both while in movement and at rest. It is actively motile, propelling itself by rotating aronnd its longitudinal axis, first in one direction and then in another.

The organism can be obtained by any of the following methods:

1. From a surface lesion (after having cleansed the part) by scraping with a sharp spoon, or by rubbing a platinum loop over the surface.

2. By withdrawing some fluid from an enlarged gland by means of a hypodermic syringe.

3. From the blood. Take 1 c.c. of patient's blood, mix with 10 c.c. of $\frac{1}{3}$ per cent. acetic acid in water, centrifugalize, and examine the deposit (Noeggerath and Staehelin's method).

Stain the film preparations with Giemsa's stain, prepared as follows (Emery): Giemsa, 10 drops; distilled water, 50 drops; carbonate of potash, 1 to 2 drops (1 to 1,000 in distilled water). Stain for one hour without heat, wash in distilled water, dry, and then mount. Under the microscope, the *Spirochæta pallida* prepared in this way is seen to be stained a rose-pink colour. As the organism is very difficult to reveal, it is necessary to work in a very good light, to use $\frac{1}{12}$-inch oil-immersion lens, and high eye-piece.

It is during the tertiary stage of the disease that the most marked pathological changes in the tissues occur.

The history of tertiary syphilis is in reality the history of the gumma. As already explained (p. 16), the gumma may occur in two forms—viz., as a diffuse gummatous formation, or in concentration, forming the anatomical gumma. Any organ in the body may be affected with one or both of these lesions. Thus, there may be a gummatous infiltration of the liver or gummata on its surface, or the two lesions may occur together.

The nervous system may be similarly affected. Thus, there may be gummata of the brain or spinal cord, or there may be a diffuse gummatous infiltration of certain areas of them.

As a general rule, the anatomical gummata show a preference for parts exposed to injury, such as the subcutaneous surfaces of bones, the capsule of the knee-joint, and the surface of the liver.

Syphilis of the Nervous System.

The toxin of syphilis probably acts upon the nervous system in two ways: (*a*) Upon the nerve elements, causing

their degeneration ; and (*b*) upon the bloodvessels, membranes, and neuroglia, causing thickening of these structures.

Among the more important changes thus induced are the following :

Syphilitic Endarteritis of the arteries at the base of the brain, which, if complicated by thrombosis, may give rise to hemiplegia.

Gummatous Meningitis.

Gummata on the brain surface.

Paralysis of the Cranial Nerves, particularly the sixth, third, and fourth, from involvement in gummatous material which is very apt to form at the base of the brain.

General Paralysis of the Insane.—According to Mott, syphilis is *par excellence* the cause of this disease. Eight general paralytics were inoculated with syphilis by Krafft-Ebing, and they all showed immunity from the disease. Mott has recorded many cases of general paralysis occurring in children afflicted with congenital syphilis.

The essential pathological changes occur in the cortex, and consist of :

(*a*) Thickening and adherence of the meninges.
(*b*) Thickening of the neuroglia.
(*c*) Thickening of the walls of the arteries.
(*d*) Atrophy of the neurons.

On removing the membranes, the surface of the brain tears away with them, leaving a characteristic worm-eaten appearance, especially marked over the frontal and central convolutions.

Tabes Dorsalis. — This also is a manifestation of syphilis. The morbid changes are, *mutatis mutandis*, the same as those found in general paralysis. The disease usually starts in the dorso-lumbar region of the cord, and involves the posterior roots and the posterior columns of both sides, sometimes extending into the lateral columns.

In cases complicated by 'Charcot's joint disease' and 'perforating' ulcer of the foot, the nerves supplying the affected parts have been found degenerated.

DISEASES OF BONE.

The structure of bone is that of a specialized connective tissue impregnated with lime-salts. The periosteum on the outside of a bone is continuous with the endosteum (marrow) of the inside, and numerous bloodvessels pass from the one to the other.

This vascular continuity explains how inflammation, beginning primarily in one structure—periosteum, bone, or endosteum—is liable sooner or later to involve all three.

General Principles.

Osteitis, or inflammation of bone, is generally the result of tubercle, syphilis, or other microbic infection.

First Stage: *Hyperæmia.*—The bloodvessels dilate, exudation of inflammatory lymph begins, and the bone assumes a pink colour.

Second Stage: *Rarefaction.*—Exudation of inflammatory lymph continues, the lime-salts are dissolved out, and the bone substance is partially absorbed, the compact tissue becoming rarefied and the cancellous still more cancellous. This rarefying process is effected in part by the action of the phagocytes, in part by the peptonizing action of bacterial toxins, and in part by the solvent action of the inflammatory lymph under high pressure.

In the dry specimen the bone at this stage presents a 'worm-eaten' appearance.

Third Stage { *Caries.* *Abscess.* *Sclerosis.*

Should the rarefying process persist long enough, the whole area of affected bone dissolves away, the result being *caries* or molecular death; and if after this the inflammatory material, consisting largely of pus, becomes imprisoned by the surrounding bone, the result is *an abscess*; if, on the other hand, the inflammatory exudate during the period of rarefaction organizes, *sclerosis* results—*i.e.*, the formation of hard, dense bone. The cancellous spaces are in this way obliterated and the medullary

cavity is filled up, this being the usual condition of the terminal portion of bone in stumps after amputation.

Acute Infective Osteomyelitis (Panosteitis).

This disease is always caused by the action of staphylococci or streptococci, the organisms entering the body either through an external wound or in consequence of some infecting focus in the mouth or throat. Lowered vitality is an important predisposing factor.

The disease presents three types, according to the position of the initial lesion, which may be either in—

(*a*) The epiphysis (acute epiphysitis) ;
(*b*) The interior of the shaft ; or
(*c*) Beneath the periosteum.

Hyperæmia, exudation, and rarefaction take place, and pus rapidly forms. If the disease begins beneath the periosteum and the pus is not let out by a timely incision, the latter spreads far and wide, leaving the bone bare and dead. In this way a portion, or, it may be, the whole shaft, of the bone perishes, the result being known as *acute necrosis of bone*. This form is generally limited to the shaft, for the disease does not usually spread to the epiphysis, which is protected by the intermediate cartilage ; the neighbouring joint also escapes as a rule.

If the disease begins in the interior of the shaft, necrosis is brought about by a strangulation of the bloodvessels combined with the toxic action of the bacterial products. This is the ordinary *acute infective osteomyelitis*. If the disease begins in the epiphysis, it is generally localized to this part, and is known as *acute epiphysitis*.

Should acute infective osteomyelitis remain untreated, *pyæmia* is very likely to develop, as the infective thrombi in the veins are liable to disintegrate and be discharged into the blood-stream as septic emboli.

Caries.

Caries is the molecular dissolution of a portion of bone, resulting from the continuation of the rarefying process of osteitis, being analogous to ulceration of the soft parts of the body. It may occur in any bone, but is commonly

met with *in the cancellous tissue* of the epiphyses, the bodies of the vertebræ, the carpus, and the tarsus. By far the commonest cause is tubercle, and when thus originating it may be regarded as a *phthisis of bone*. When dead bone separates, it does so by caries taking place in the adjacent sides of the surrounding living bone.

Dry Caries.—The absorption of bone resulting from pressure—*e.g.*, of an aneurism—is sometimes spoken of as 'dry caries.' The process is of the nature of an atrophy.

Necrosis.

Necrosis is the death of bone in mass, and is analogous to gangrene of the soft parts. It commonly affects the *compact tissue* of the shafts of the long bones. In all cases the cause is a cutting off of the blood-supply, either by injury or inflammation (periostitis, osteitis, or osteomyelitis). Necrosed bone is bloodless, dry, and white in colour, but on exposure to the air it often becomes brown.

Separation of Dead Bone.—The surrounding bone becomes inflamed, caries results, and the loosened dead bone, now called a *sequestrum*, lies bathed in pus in a cavity lined with granulation tissue. The periosteum covering the sequestrum may form a new layer of bone over it—the *involucrum*—and this is perforated by holes —*cloacæ*—to allow of the escape of pus.

Tuberculosis of Bone.

Tubercle may form in the periosteum, in the epiphyses, or in the substance of the diaphyses. Its favourite position is the *cancellous tissue* of the epiphyses, the bodies of the vertebræ, the carpus, and the tarsus—in other words, bone in the neighbourhood of a joint.

Syphilitic Diseases of Bone.

In the *secondary stage* of syphilis a fleeting periostitis may occur.

In the *tertiary stage* the bone affections which may occur are similar to those characterizing this stage of the disease elsewhere—viz., the development of gummatous

material either in the form of definite *gummata* or as a *diffuse infiltration*. In this way gummatous material may form in either the periosteum or the bone, resulting in *caries*, *necrosis*, or *sclerosis*. These pathological changes may be combined in various ways: thus, caries and necrosis may occur together (*cario - necrosis*), and a gumma may be surrounded by hard, sclerosed bone. Gummata are most likely to form on parts exposed to injury, and hence they are most often met with on the subcutaneous surfaces of bones. Syphilitic caries is commonest in the skull. Syphilitic sclerosis may be widely diffused throughout the whole shaft of a long bone, and it also occurs in the bones of the cranial vault.

In both acquired and congenital syphilis the fingers and toes may be affected with periosteal gummata, giving rise to the condition known as *syphilitic dactylitis*.

In *congenital syphilis* the diseases of bone, according to Parrot, assume two principal forms:

1. Atrophic { (*a*) Gelatiniform. (*b*) Osteochondritis.
2. Hypertrophic or Osteophytic { (*a*) Osteoid. (*b*) Fibro-spongioid.

In *gelatiniform atrophy* the bone tissue is replaced by a gelatinous substance.

In *osteochondritis* (sometimes called syphilitic epiphysitis) the cartilage intermediate between the epiphysis and the diaphysis becomes abnormally thick and loses its regular outline; ossification stops short at calcification, the zone of calcified material being dense and brittle; as a result, fracture is liable to occur, and as the symptoms may resemble paralysis, Parrot has named this condition *syphilitic pseudo-paralysis*.

In the hypertrophic variety the new bone may be hard and ivory-like, when it is termed *osteoid*; or it may be fibroid in structure and very vascular, when it is termed *fibro-spongioid*. The two conditions may be combined; thus, the osteoid variety may be arranged in layers, with fibro spongioid material between them. The most common sites for these changes are the ends of the humerus, femur, and tibia.

In the skull 'bosses' of new bone may form around the fontanelles ('Parrot's nodes'), and these may become

bridged over, and so give rise to the rounded, prominent forehead observed in later life in subjects of this disease. In the occipital and parietal bones circumscribed areas of extremely thin bone, or even of membrane only, are sometimes met with. To this condition the name of *craniotabes* has been given. (In the Museum of the Royal College of Surgeons, London, are specimens presented by M. Parrot showing all these changes.)

Tumours of Bone.

The usual primary tumours of bone are the enchondromata, the osteomata, and the sarcomata. Secondary tumours may be either sarcomatous or carcinomatous.

Sarcomata of Bone.—In descending order of malignancy these tumours stand thus:

1. Periosteal sarcoma.
2. Endosteal sarcoma of diaphysis.
3. Endosteal sarcoma of epiphysis.

The last named is usually the 'myeloid' variety, the favourite sites of which are the lower ends of the femur and radius, the upper ends of the tibia and humerus, and the lower jaw. *Periosteal sarcoma is of extreme malignancy.* Myeloid sarcoma never causes secondary growths.

Rickets.

Rickets, first described by Glisson in 1650, is a blood disease affecting the nutrition of the entire organism, but as its most obtrusive pathological effects are registered in the bones, it comes in for consideration here. Sir William Jenner said it would be as reasonable to regard rickets as a disease of the bones only as it would be to regard typhoid fever as merely a disease of Peyer's patches. The condition commonly attracts attention at about the sixth month after birth. There is probably no such thing as congenital rickets. The constitutional symptoms strongly suggest a *toxæmia*: the child is anæmic; it is very irritable, and cries when handled, on account of a diffuse tenderness of the body; it is restless during sleep, sweats freely about the head, and a slight degree of fever is often present. There is also a tendency

to inflammation of mucous membranes, notably of those lining the alimentary and respiratory tracts.

The essential cause is probably *a toxin generated in the alimentary canal as the result of improper feeding*. The toxin, being absorbed into the system, perverts nutrition, particularly in places where developmental activity is great—*e.g.*, in the growing parts of bones. Lack of fresh air and sunlight is a contributory cause.

The salient pathological feature in the bones is defective calcification—*i.e.*, the lime-salts are not laid down in the newly-formed bone in sufficient quantity.

The most characteristic changes occur at the epiphyses and beneath the periosteum of the long bones. Thus the cushion of cartilage between the epiphysis and the diaphysis is thicker than normal, and the plane of ossification on the diaphyseal side of the cartilage, instead of being even, is irregular. The cartilage cells divide with excessive rapidity. The newly-formed bone is unduly soft, chemical examination showing it to be very deficient in lime-salts.

Similar changes take place beneath the periosteum, the new bone laid down by this membrane being softer and more spongy than in health, and as a consequence the bones bend, giving rise to various characteristic deformities. These are more marked in some bones than in others, although the entire osseous system is affected.

The anterior fontanelle remains open longer than the normal eighteen months after birth, and the teeth erupt late. From pressure by the pillow soft, decalcified areas are liable to form in the occipital and parietal bones (=craniotabes), though this condition generally (some say always) indicates congenital syphilis.

If the child lies much on its back, the occipital bone is liable to become flattened and the frontal bone prominent; for the bones of the cranium are easily displaced, on account of the late closure of the fontanelles and the yielding nature of the sutures. The cranial vertex is flat, and the coronal suture may be 'keeled.'

In the spine there is usually some kyphosis, and the child may not begin to sit up until after the first year, instead of, as normally happens, at about the seventh

month. The sternum is thrown forward ('pigeon-breast'), and there is considerable thickening of the ribs at their junction with the cartilages ('beaded' ribs). It should, however, be remembered that a small degree of beading is normal.

Rickets is the commonest cause of deformed pelvis. The sacral promontory projects forwards from the downward pressure of the weight of the body, and the brim is kidney-shaped.

The most notable changes in the long bones are enlargement at the junction of the shaft with the epiphysis, exaggeration of the normal curvatures, and the development of curves due to the traction of powerful muscles—*e.g.*, an outward curve of the humerus, corresponding to the insertion of the deltoid. The bones of the forearm are bent outwards in their lower thirds. The femur shows a long forward curve. The bones of the leg are bent outwards and forwards in their lower thirds. Strong bony buttresses usually develop in the concavities of the curvatures.

The tendency of the disease is towards spontaneous cure, *the bones in course of time becoming properly ossified in their deformed positions.*

Achondroplasia.

This disease is due to imperfect ossification of the *epiphyseal cartilages*. It is sometimes inaccurately called fœtal rickets, differing from ordinary rickets in that it is always *congenital*. The bones which develop from cartilage are alone affected.

The development *in length* of the diaphyses of the long bones is defective though they are normal in thickness, so that the limbs are short and stunted. There is no bending, and there are no abnormal curves. The bones at the base of the skull ankylose early, and as those at the vault grow naturally, the head looks unusually big. The bridge of the nose is depressed. The bones which develop from membrane being unaffected, the clavicles, ribs, sternum, and vertebral column are all of normal size. Death occurs in most cases a few days after birth, and those who survive grow up dwarfs.

Osteomalacia (Mollities Ossium).

This disease is essentially one of *decalcification*, the lime-salts being absorbed and the bones in consequence becoming soft, bent, and liable to spontaneous fractures which do not unite. The disease is almost entirely confined to women, and generally develops during pregnancy. The bones usually affected are those of the *pelvis*, the *vertebral column*, and the *ribs*.

The morbid change begins in the interior of the bone, the medulla being replaced by a tissue resembling the splenic pulp. The decalcification proceeds from within and spreads outwards, until at length all that is left of the original bone is a thin layer of compact tissue beneath the periosteum. As in a few cases removal of diseased ovaries has resulted in arrest of the disease, it has been suggested that the solution of the bone-salts which takes place in it may be due to the action of an abnormal ovarian secretion.

Osteitis Deformans.

This disease was first described by Sir James Paget. 'The disease affects most frequently the long bones of the lower extremities and the skull, and is usually symmetrical. The bones enlarge and soften, and those bearing weight yield and become unnaturally curved. The spine may sink and seem to shorten, with greatly increased dorsal and lumbar curves; the pelvis may become wide; the necks of the femora may become nearly horizontal, but the limbs, however misshapen, remain strong and fit to support the trunk' (Paget).

The calvarium may become enormously thickened, the patient noticing that he has to use larger and larger hats, while his stature becomes less and less. The disease begins after middle life, and its progress is very slow, sometimes lasting as many as twenty years. The enlargement and softening of the bones are due to the development of soft, spongy, and highly vascular new bone.

Acromegaly.

This disease is characterized by excessive growth of the *bones* of the hands, feet, and face, together with enlarge-

ment of the features and the tongue. The lower jaw is increased in size and projects forwards ; the supra-orbital ridges are prominent (see p. 109).

Leontiasis Ossea.

In this disease the bones of the face and cranium become greatly thickened.

Hypertrophic Pulmonary Osteo-Arthropathy.

This disease is characterized by enlargement of the *terminal phalanges* of the fingers and toes and neighbouring bones, with incurvation of the nails. It is associated with bronchiectasis, empyema, and pulmonary tuberculosis, and is probably caused partly by absorption of toxic material from the diseased lung or pleura, and partly by the sluggishness of the circulation resulting from the pulmonary obstruction.

DISEASES OF JOINTS.

Tuberculosis of Joints.

Tuberculosis of a joint may be compared with tuberculosis of the lung. The disease may begin in the synovial membrane, which is the morphological equivalent of the pleura (tubercular synovitis), or it may begin in the head of the bone, which is the morphological equivalent of the lung (tubercular osteitis). It never begins in the arthritic cartilage.

Tubercular synovitis affects, as a rule, the hinge-joints —viz., the elbow, wrist, knee, and ankle. Tubercles form in the synovial membrane, causing it to become thickened, gelatinous, and pulpy. The synovial fringes spread over the articular surfaces, covering them like a veil, and from the under surface of this veil small processes penetrate into the underlying cartilage, a condition compared by Billroth to ivy creeping over a wall and becoming gradually attached by its roots. The cartilage now becomes ulcerated, and finally, unless the tubercular process is arrested, the underlying bone is invaded and undergoes caries.

Owing to caseation and suppuration of the tubercular material, the entire synovial membrane is converted into a pyogenic membrane similar to that found in a chronic tubercular abscess, the pus eventually burrowing to the exterior. The whole interior of the joint in this way becomes disorganized.

Tubercular osteitis affects the ball-and-socket joints, and is well illustrated in the case of hip-joint disease. The process here usually starts in the epiphysis of the femur, either close to the intermediary cartilage or just beneath the articular cartilage. Caries supervenes, and the inflammatory products escape into the articular cavity, the synovial membrane and ligaments becoming secondarily affected and the whole joint tending to disorganization, the acetabulum being inoculated by contact with the carious head of the femur. In some cases the epiphysis becomes detached and lies loose in the joint. The pus generally escapes through the thinnest part of the capsule—*i.e.*, at its posterior part. It then burrows forwards beneath the gluteus minimus, the medius, and the tensor vaginæ femoris, and ultimately forms a swelling beneath the anterior superior iliac spine.

Complications of Tuberculous Joints.—If an abscess bursts and its interior becomes septic, *amyloid disease* is likely to develop. At any time during the progress of tuberculosis in a joint *acute miliary tuberculosis* (either of the pia mater, lungs, or abdominal viscera) may be set up.

Complete disorganization does not of necessity follow in all cases of tuberculous joints. In favourable cases, and if treatment has been begun early, the disease may be arrested, the inflammatory products being in part absorbed and in part converted into fibrous tissue.

In rare cases tuberculosis of a joint starts from a *tuberculous periostitis*, or from a *tuberculous bursa*.

Rheumatoid Arthritis, or Osteo-Arthritis.

This term embraces several clinical types. The cause, in certain of them at least, is *probably a toxin*, acting either directly on the joint structures or on the nerves supplying these parts. In the more chronic form, coming

on generally after middle life, the disease is characterized by changes occurring in—

(*a*) *The articular cartilages.*
(*b*) *The underlying bones.*
(*c*) *The synovial membrane.*
(*d*) *The inter-articular ligaments.*
(*e*) *The surrounding muscles.*

The hyaline matrix of the *articular cartilage* becomes fibrillated, and the cartilage cells proliferate and escape into the joint. The surface of the cartilage now loses its polish, assuming a velvety appearance, and in course of time its central part is worn down, and the underlying bone, which is seen to be highly polished—like porcelain or ivory—is exposed.

While these changes are in progress, the circumference of the cartilage becomes irregularly thickened ('lipping'), sometimes developing flange-like outgrowths, or *ecchondroses*, which have been likened to the gutterings of a wax candle. These ecchondroses may in course of time become ossified, when they are known as *osteophytes*.

The *synovial membrane* thickens, its fringes hypertrophy, and finally the whole membrane may assume a shaggy appearance. Occasionally nodules of cartilage develop in the fringes, and these sometimes break off, forming 'loose bodies' in the joint.

The *inter-articular ligaments* in course of time degenerate and wear away. In this way the ligamentum teres disappears from the hip-joint, the intra-capsular part of the long tendon of the biceps from the shoulder, and the crucial ligaments and inter-articular cartilages disappear from the knee.

The *muscles around the joint* tend to atrophy, a change often well marked when the disease attacks the shoulder or hip.

The above changes are all typically seen in *morbus coxæ senilis*, but they are also observed in that symmetrical polyarticular chronic articular affection (involving, it may be, all the joints in the body) for which Garrod would reserve the term *arthritis deformans*. The enlargements of the end joints of the fingers met with in this disease are known as Heberden's nodes.

This affection must, clinically at least, be distinguished from another polyarticular affection to which Garrod would limit the term *rheumatoid arthritis*, because the joint affection in it is genuinely rheumatoid in character. The disease generally comes on in early adult life, involving many joints symmetrically. All the joints of the body may be affected. (N.B.—In gout and rheumatic fever the temporo-maxillary joints and cervical spine are practically never attacked.) Those of the fingers are apt to be involved early, causing these latter to be fusiform from swelling of the inter-phalangeal joints. Hence the disease is sometimes known as the *fusiform* variety of rheumatoid arthritis. The joint affection is peri- rather than en-arthritic, though enarthritic changes, somewhat similar to those observed in arthritis deformans, may in course of time occur, for which reason some hold that the two diseases are fundamentally the same. The muscles about the affected joints undergo marked atrophy, and the contractions of the wasted muscles may cause considerable crippling.

A feature of this malady is its constitutional nature. It is manifestly a blood disease. The patient is anæmic, his vitality is low, and he is apt to be febrile.

Still's Disease is allied to the last, if it is not actually the same, but, in addition to the joint affection, enlargement of the spleen and of the lymphatic glands is apt to occur. It is met with in children.

The Blood in Rheumatoid Arthritis.

Bullmore and Waterhouse (*Edin. Med. Journ.*, June, 1907) publish the results of an investigation into the condition of the blood in a series of forty-two cases of rheumatoid arthritis. (*a*) *Hæmoglobin:* In only one case was the percentage of hæmoglobin 100. In eight it was between 90 and 100, in twelve between 80 and 90, in eleven between 70 and 80, in four between 60 and 70, and in one 30. (*b*) *Red blood cells:* In all but nine cases the number of red cells was below 5,000,000 per cubic millimetre, in twenty it was between 4,000,000 and 5,000,000, in ten between 3,000,000 and 4,000,000, and in one only 2,890,000. The microscopical appearances were those of a secondary anæmia of greater or less degree. The colour index varied from 0·72 to slightly over normal. The constancy in the number of white corpuscles was remarkable; in all but six instances it was between 5,000 and 10,000. Except in one case, the differential leuco-

cyte count showed physiological proportions between the various forms. Myelocytes were present in a few cases.

Neuropathic Arthritis.

This group of joint diseases is found in connection with certain diseases of the spinal cord and nerves, the most notable lesions being: tabes dorsalis, syringomyelia, spina bifida, hemiplegia, paraplegia, peripheral neuritis, and division of peripheral nerves.

Charcot's Joint Disease develops in connection with *tabes dorsalis*, generally during the pre-ataxic stage. The usual joints to be affected are those of the knee, hip, and shoulder. The onset is generally sudden; there is considerable swelling of the joint, but neither pain nor fever. A patient may go to bed well, and wake up in the morning with the joint distended without apparent cause.

This swelling is due in part to effusion into the joint, and in part to œdema of the soft tissues outside it (the 'œdema without pitting' of Charcot).

Although in a few cases the effusion may be absorbed (the 'benign' form of Charcot), the articulation returning to its normal state, it generally proceeds to rapid and complete non-inflammatory destruction of the articulation (the 'malign' form of Charcot), and culminates in the production of a 'flail joint' movable in all directions, or in dislocation.

It is essentially a trophic lesion, the nerves going to the joint being found diseased.

The morbid changes characterizing it are: effusion into the joint, early disappearance of the ligaments and cartilages, and *great atrophy of the articular ends of the bones.*

Osteophytes may form, sometimes in large numbers. In Charcot's disease of the knee it is not uncommon to find *bursal swellings*, especially of the bursa which so frequently communicates with the joint—viz., that under the semi-membranosus tendon.

Syringomyelia may be associated with a form of joint disease similar to that occurring in tabes dorsalis, but the seat is *usually in the upper limb.* In this disease trophic lesions may be also found in the skin, such as *whitlows*,

ulcers, and *gangrene* of the fingers. The pathology is the same as that observed in Charcot's joint disease.

Sometimes the joint affection in syringomyelia is similar to that characteristic of arthritis deformans.

Gonorrhœal Rheumatism.

This disease, which is sometimes called *young man's rheumatism*, is caused by the entrance into a joint of the gonococcus, cultivations of this organism from the effusion in the affected joint having been made in numerous cases. One or several joints may be affected, as also sometimes fasciæ, tendon sheaths, bursæ, and the fibrous sheaths of nerves. The knee is most often attacked, the elbow, ankle, and wrist being other frequent sites. A very troublesome form is that which affects the ankle, the tarsal joints, and the fibrous structures in the sole, causing a severe form of flat-foot. The disease seldom sets in until the third or fourth week after contagion, and it may be either *acute*, *subacute*, or *chronic*.

In the *acute* form there may be suppuration, and even complete disorganization of the joint. The more common *subacute* or *chronic* form is characterized by a plastic exudation involving the ligaments and *peri-articular structures*, and there is a marked tendency to the formation of new fibrous tissue, which leaves the joint permanently stiff. In those cases in which the larger joints are affected the patient may become quite crippled. Sometimes the disease simulates rheumatic fever.

DEFORMITIES.

Branchial Fistula, Cleft-Palate, and Hare-Lip.

In order to understand the nature of these deformities it is necessary to recall some points in the normal development of the upper jaw and neighbouring parts. In early fœtal life the anterior portion of the alimentary tube communicates with the exterior on either side by a number of slit-like openings—the *branchial clefts*, between which are the *branchial arches*. The first branchial cleft persists as the external auditory meatus,

the tympanum, and the Eustachian tubo. All the others should close. In some rare cases, however, the third or fourth remains partially unclosed, the result being a fistula (*branchial fistula*) opening on the surface of the body near the sternal head of the sterno-mastoid muscle. Similar fistulæ have also been met with below the glottis.

As development proceeds, the *first branchial arch* on either side *divides*, forming the two superior and the two inferior maxillary processes. The two inferior processes unite in the middle line to form the lower jaw and the lower lip.

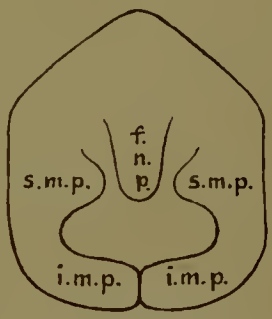


FIG. 7.

The two superior processes grow forwards to form the superior maxillæ, with the hard and the soft palate, the cheeks, and the lateral parts of the upper lip. They do not, however, unite anteriorly, but between them there grows downwards from the front of the skull the *naso-frontal process*, from which are developed the nose, the vomer, the nasal septum, the premaxillæ carrying the incisor teeth and the central portion of the upper lip.

These various parts should unite by the ninth week of fœtal life; should union be defective, the following deformities may occur:

1. Bifid uvula.
2. Fissure of the soft palate, with bifid uvula.
3. Fissure of both the soft and the hard palate.
4. Fissure of the hard palate only (very rare).

5. Fissure of the hard and the soft palates, combined with fissure of the alveolus and the lip on one side.
6. The same as 5, with fissure of the alveolus and lip *on both sides*.
7. Simple hare-lip.
8. Double hare-lip.

In the rare case of cleft of the hard palate the nasal septum is usually attached to one side of the palate, shutting off the nose from the mouth on that side. In only very rare cases is the lower border of the nasal septum free, so that *both* nasal cavities communicate with the mouth.

In double hare-lip the premaxilla and the central portion of the upper lip may be carried forwards as an appendage of the nose.

Very rarely, the fissure of the hare-lip extends upwards on one side of the nose towards the inner side of the orbit (*patent orbital groove*).

Meningocele and Encephalocele.

A **meningocele** is a protrusion of the *dura mater* and the *arachnoid* through a congenital aperture in the skull, where it forms a soft fluctuating swelling, which contains cerebro-spinal fluid, and which increases in size on expiration, coughing, or crying. The most common site is the occipital bone, just above the foramen magnum, but it may also occur in the anterior fontanelle, at the root of the nose, at the base of the skull (protruding into the nasal passages or pharynx), and at the external angle of the orbit. It is often associated with hydrocephalus.

An **encephalocele** is a meningocele containing brain substance. It pulsates with the heart-beat.

A **hydrencephalocele** is an encephalocele enclosing a cavity filled with fluid continuous with that in the ventricles.

Spina Bifida.

Spina bifida is a congenital defect of the posterior part of the spinal canal, due to arrested development of the laminæ of one or more vertebræ, and generally accom-

panied by protrusion of the meningos and cord through the gap, in the form of a cystic tumour which varies in size from a walnut to an orange. The usual position is the *lumbo-sacral region*, as the laminæ of this part are the last to close in fœtal life. It is sometimes associated with hydrocephalus and talipes.

Varieties.—Meningocele, meningo-myelocele, syringo-myelocele, myelocele.

A *meningocele* consists of a protrusion of the dura mater and the arachnoid through the gap in the spinal canal; it contains cerebro-spinal fluid.

A *meningo-myelocele* is the most common form of spina bifida. It consists of a meningocele plus the spinal cord and nerves.

A *syringo-myelocele* is rare. It is similar to the last, but the central canal of the spinal cord is distended, the posterior part of the cord being spread out over the interior of the sac.

A *myelocele* is the condition resulting from non-closure of the primitive medullary groove, the central canal opening on the surface.

Torticollis.

Torticollis is a deformity caused by contraction of one of the sterno-mastoid muscles, by which the head is drawn downwards towards, and rotated away from, the affected side.

The deformity may be congenital, or it may appear soon after birth. In the former case it is due to an arrest of development, and in the latter to partial rupture of the sterno-mastoid during the third stage of labour. In childhood it may come on after measles and scarlatina, usually as the result of inflamed cervical glands. In some cases it arises from irritation of the spinal accessory nerve. Occasionally it is *spasmodic*, disappearing when the patient is anæsthetized.

If torticollis lasts for any length of time, the deep cervical muscles and the anterior portion of the trapezius become shortened, and the cervical vertebræ rotated, and lateral curvature of the spine may set in.

The congenital variety, unless surgically treated, tends to produce asymmetrical growth of the head.

Lateral Curvature of the Spine.

This deformity commonly results from *weakness of the spinal muscles*, and commences in almost all such cases at about the period of puberty. It may also be due to the shortening of a limb or the falling in of the ribs after an empyema. There is a *primary curve*, generally in the dorsal region and convex to the right, with *secondary* or compensatory curves above and below, in a direction opposite to that of the primary curve and with the object of maintaining the body in the upright position. In addition to the lateral curvature, *the vertebræ are rotated on their vertical axes*, the front of their bodies moving towards the convexity of the curve and the spines towards the concavity. In this way the ribs on the convex side are thrown backwards and widely separated, while on the concave side they are thrown forwards and crowded together.

If the condition remains untreated, the inter-vertebral discs become permanently wedge-shaped, the base of the wedge being directed towards the convexity of the curve. In old-standing and advanced cases the bodies of the vertebræ also become wedge-shaped.

Lateral curvature is common in Friedreich's disease and in syringomyelia.

Angular Curvature of the Spine.

This deformity, also called Pott's curvature, is caused by the destruction of one or more of the bodies of the vertebræ by *tubercular caries*. The disease may occur in any part of the spine, but its usual starting-point is the *dorso-lumbar region*, the caries beginning either beneath the periosteum on the anterior surface of the vertebral bodies, or in the cancellous tissue of their interior. The affected bodies and adjacent inter-vertebral discs being destroyed, a gap is left, and the upper part of the spinal column then falls forwards upon the lower to form an angle—the so-called 'angular curvature of the spine.'

If repair takes place, the gap is filled in by a buttress of new bone or by fibrous tissue, and at the same time the

laminæ and spines of the neural arches usually become ankylosed, and so act as a kind of splint.

Spinal abscess is the usual accompaniment of caries of the vertebræ. As the pus accumulates it travels along the lines of least resistance, either following the course of a bloodvessel or burrowing beneath fasciæ. When the disease is seated in the cervical region the pus may point in the pharynx (*post-pharyngeal abscess*), or pass along the back of the œsophagus into the posterior mediastinum, or it may work its way into the posterior triangle of the neck, and even sometimes extend into the axilla.

When the disease is seated in the upper- or the mid-dorsal region, the pus usually passes backwards along the posterior branches of the intercostal arteries, and forms a swelling close to the spinous processes (*dorsal abscess*). When the disease is seated in the lower dorsal or lumbar region, the pus may pass backwards and form a swelling just external to the erector spinæ muscle (*lumbar abscess*).

As a rule, however, when the disease attacks the dorso-lumbar region, the pus burrows into the psoas muscle and forms a

Psoas abscess, the course of which is determined by the attachments of the ilio-psoas fascia.

The ilio-psoas fascia, which invests both the psoas and the iliacus muscles, is attached above to the ligamentum arcuatum internum, below to the iliac crest and brim of the true pelvis, internally to the front of the bodies of the lumbar vertebræ, externally to the transverse processes of the same vertebræ, and it ultimately follows the ilio-psoas tendon to its insertion into the small trochanter of the femur.

The abscess destroys the psoas muscle, extends downwards into the false pelvis over the iliacus muscle, and forms a large fluctuating swelling in the iliac fossa. Extending still further, the pus travels by a narrow neck beneath Poupart's ligament, just external to the femoral vessels, and then works its way behind the femoral vessels towards the insertion of the ilio-psoas tendon into the small trochanter of the femur, pointing at or close to the saphenous opening.

A typical psoas abscess, then, when fully developed, consists of four parts: a narrow track in the psoas muscle, an expanded portion over the iliac fossa, a narrow neck

beneath Poupart's ligament, and a second expanded portion in the upper part of the thigh. Occasionally the psoas abscess is double.

In some cases the pus tracks down the thigh, and it has been known to travel as low down as the popliteal space, and even as far as the side of the tendo Achillis.

Occasionally the pus may enter the true pelvis, pass through the great sacro-sciatic notch, and form a gluteal abscess, or it may work its way along the side of the rectum and point in the ischio-rectal fossa.

Paraplegia occurs in but a small percentage of cases of angular curvature, the spinal cord generally escaping compression because the bending of the vertebral column takes place slowly ; also because the spinal canal is considerably larger than the cord, which, moreover, is protected by the dura mater. When paraplegia does occur, the cause is pachymeningitis, or the pressure of inflammatory products. These tend to become absorbed in process of time ; hence the paraplegia is rarely permanent.

Talipes.

Deformities of the foot may be congenital or acquired, and they may occur in both extremities or in one only. The following are the different varieties :

Talipes Equinus, in which the heel is drawn up so that the patient walks on his toes, which are at a right angle to the foot. This condition is rarely congenital, and is due either to infantile paralysis of the extensor muscles causing a shortening of the muscles at the back of the leg, or it has been known to result from an abscess in the calf.

Talipes Calcaneus, in which the anterior part of the foot is drawn up, forcing the patient to walk on the heel. It may be congenital, or the result of infantile paralysis of the flexor muscles of the calf. It is very rare.

Talipes Varus, in which the anterior part of the foot is twisted inwards at the calcaneo-cuboid and astragalo-scaphoid articulations, the patient walking on the outer border. It is generally associated with talipes equinus, pure talipes varus being of extreme rarity, and, when found, usually congenital.

Talipes Valgus, in which the anterior part of the foot

is twisted outwards at the calcaneo-cuboid and astragalo-scaphoid articulations, the plantar arches being obliterated and the sole flattened. It may be either congenital or acquired, and when the latter is generally the result of infantile paralysis.

Talipes Equino-Varus, in which the heel is drawn up and the foot twisted inwards, the patient walking on its outer border, where a bursa tends to form. The twisting takes place at the calcaneo-cuboid and astragalo-scaphoid articulations. In ordinary cases there is an increase in the obliquity of the neck of the astragalus.

Secondary contraction of the muscles, ligaments, and fasciæ takes place on the concave side of the foot. The tendo Achillis and the tendons of both the tibialis anticus and the tibialis posticus are shortened.

With the exception of the altered obliquity of the neck of the astragalus just mentioned, the tarsal bones at first are quite normal, but those on the inner side of the foot, being compressed, remain undeveloped in old-standing cases.

The deformity is generally congenital, and affects both feet. The most probable explanation of this form of talipes is that, owing to some malposition of the fœtus *in utero*, or deficiency of liquor amnii, or the presence of adventitious bands, there is *an arrest of the unfolding process of the feet.*

'If the inversion of the foot, which is normal during the early periods of fœtal life, be maintained beyond the normal period of time, the muscles and ligaments will as a consequence be adaptively short on one aspect of the limb, and too long on the other; a normal position of inversion will finally become a deformity' (Parker and Shattock).

If this form of talipes develops after birth, it is probably due to infantile paralysis. It is much the most frequent variety of talipes.

Talipes Calcaneo-Valgus, in which there is a combination of talipes calcaneus with talipes valgus. It is a very rare deformity.

Talipes Cavus, in which the main arch of the foot is abnormally developed. It is always an acquired condition, and is due to paralysis of the interossei muscles, with tonic contraction of the opposing muscles, in consequence of

which the first phalanges become hyperextended upon the metatarsal bones, and the last two phalanges flexed towards the sole.

The deformity is almost always combined with either talipes equinus or talipes equino-varus.

Flat-Foot, or Talipes Planus.—The plantar arches are not present in the infant, but are acquired by exercise of the deep muscles at the back of the leg (flexor longus digitorum, tibialis posticus, and flexor longus hallucis), together with that of the tibialis anticus and the peroneus longus. The ligaments (more particularly the inferior calcaneo-scaphoid and the long and short plantar ligaments) simply help to keep the bones in position when the arch is finally established.

The primary cause of flat-foot would appear to be *muscular weakness;* this throws an extra strain upon the ligaments, which, relaxing, allow the instep gradually to sink, so that the sole becomes quite flat, with a tendency to eversion of the foot. The head of the astragalus, which forms the keystone to the main plantar arch, is displaced downwards, and in bad cases may rest upon the ground, the internal malleolus being perceptibly lowered. The inner side of the foot becomes lengthened.

The deformity generally comes on in early adult life, when the body-weight increases out of proportion to muscular development, and it is especially liable to occur if the patient has to carry a heavy weight, as, for instance, a girl to carry an infant.

Genu Valgum, or '**Knock-Knee,**' is a deformity in which the tibia is deflected outwards from the femur, so that the external angle at the junction of the leg with the thigh is smaller than normal.

The deformity is *always acquired*, and usually double.

Knock-knee develops at two periods of life—

(*a*) During early childhood.
(*b*) During adolescence.

(*a*) *During Early Childhood.* — The cause here is *rickets.* The lower end of the diaphysis of the femur and the upper end of the diaphysis of the tibia, being soft, bend. The result is an *apparent* lengthening of the internal condyle of the femur.

(*b*) *During Adolescence.* — The strength of the knee-joint, like that of the arch of the foot, depends not only upon the ligaments but also on the bracing action of the surrounding muscles. Normally, the weight of the body is transmitted more through the outer than the inner condyle of the femur, but if the muscles are weak, the weight is unduly thrown upon the outer condyle, the growth of which is retarded, while that of the inner is accentuated.

In whichever way the deformity of knock-knee is produced, there is stretching of the internal lateral ligament and shortening of the external lateral ligament, the ilio-tibial band of the fascia lata, and, the biceps; the patella also is thrown outwards.

Hallux Valgus consists of an outward displacement of the great toe, the result of wearing faultily-shaped boots. As a consequence, the toes are crowded together and the head of the first metatarsal bone becomes prominent, being usually covered by a bursa (*bunion*).

Hammer-Toe is the deformity in which there is hyper-extension of the first phalanx, with flexion of the second and extension of the third. Corns or bursæ usually form over the points of pressure. The deformity generally occurs in the second toe.

Although sometimes congenital, it is usually acquired as the result of a hallux valgus crowding the toes together, or from wearing pointed boots or high heels.

Dupuytren's Contraction is a shortening of the digital processes of the palmar fascia inserted into the second phalanges, the result of a chronic inflammatory change. It commonly begins in the little finger, thence extending to the ring and middle fingers, which are drawn down into the palm.

The cause is generally some long-continued pressure on the palm of the hand, as in the use of certain tools, the playing of golf, rowing, and the leaning on a walking-stick. In some cases contraction develops without any apparent exciting cause, and it is then ascribed to gout or rheumatism.

On examining the hand, projecting ridges can be felt extending from the palm to the fingers, and if an attempt is made to straighten the fingers, these ridges become

taut. The skin over them is at first free, but subsequently becomes adherent.

The deformity can be readily diagnosed from contraction of the flexor tendons by the fact that the tendons above the wrist do not become tense when an attempt is made to straighten the fingers.

Adenoid Disease.

Adenoid disease ('adenoids') consists of a hypertrophy of the adenoid tissue in the naso-pharynx. The growth may entirely fill this cavity, causing a blockage of the Eustachian tubes and of the posterior nares, thus rendering mouth-breathing necessary.

The disease, though it is said to be sometimes congenital, does not generally begin until after the first year of life. It rarely begins after puberty, and if already existing at puberty, tends spontaneously to get well after this period.

Should the nasal passages be chronically blocked before the upper jaw (maxilla) has finished growing, this latter fails to develop properly, and there results what may be termed 'the mouth-breather's jaw.'

The Mouth-Breather's Jaw.—This deformity essentially involves the maxilla, the mandible being affected only in so far as its shape is moulded by that of its fellow. This fails to grow to its normal dimensions, and it is compressed laterally, so that the front portion projects unduly while the palate is vaulted, and though in reality less than the normal height, appears abnormally high.

The alveolar ridge being less than the normal length, while the teeth tend to grow to their normal dimensions, these are unable to take up their proper positions, and are thus irregularly disposed. Pronounced dental irregularity, indeed, is pathognomonic of the mouth-breather's jaw.

Defective development of the maxilla leads to alteration in the shape not only of the mandible, but even of the skull.

Though adenoid disease is much the most frequent cause of nasal blockage in the young, and thus of the mouth-breather's jaw, children may, of course, suffer from nasal obstruction from other causes, so that a typical

mouth-breather's jaw may sometimes be met with in a person who has never suffered from adenoids, but this is rare. Congenital syphilis, being a cause of nasal obstruction, may lead to the deformity; in this case, however, owing to the imperfect development of the teeth, dental irregularity is less apt to occur.

The pathology of this deformity has excited much controversy. Probably the chief factor in its production is a negative one—*i.e.*, the absence of the normal stimulus supplied by nasal breathing. Clearly the daily passage of some fifty thousand respiratory currents through the nose must influence the development of the surrounding parts.

Adenoids is essentially a disease of civilized peoples. That it must be very rare among primitive communities is shown by the fact that among the vast collection of skulls belonging to such in the Hunterian Museum not a single mouth-breather's jaw is to be found.

One known factor in the production of adenoids is catarrh of the naso-pharynx. Now, catarrh is often microbic in origin, and the frequency of adenoids among the civilized may perhaps partly be explained by the frequency with which they suffer from infective 'colds in the head,' owing to their being so much crowded in microbe-infected dwellings. A much more potent cause of catarrh in children, however, is improper feeding, leading to toxæmia of gastro-intestinal origin—indigestion toxæmia, as we may call it. Improperly-fed children suffer greatly from gastritis, enteritis, bronchitis, pharyngitis, and rhinitis. The chief defect in the 'modern' system of feeding children is that their food contains an excess of pultaceous starchy material, and does not afford sufficient exercise for the jaws. In consequence of this, not only does the child suffer from perennial indigestion toxæmia, with the consequent tendency to catarrh, but the jaws and neighbouring parts, including the nasal apparatus, fail to develop properly. Now, an ill-developed naso-pharynx, lined by a catarrhally-disposed mucous membrane, affords conditions favourable to the growth of adenoids. The absence of the normal stimulus to the flow of blood and lymph in this region afforded by vigorous mastication is a further factor in causation, and in this connection the

close proximity of the powerful pterygoid muscles to the naso-pharynx is not without significance.

Adenoid disease is, in short, essentially a dietetic disease, and might be practically eradicated by the adoption of a rational system of feeding children.

The like is also true of most dental diseases—notably dental caries and pyorrhœa alveolaris, both of which might be greatly lessened if the jaws and teeth were adequately exercised.

Pyorrhœa alveolaris is a purulent inflammation of the peri-odontal membrane—*i.e.*, the periosteum lining the interior of the alveolus. This membrane becomes invaded with pyogenic cocci, and pus forms between it and the fang, causing the tooth to loosen and ultimately to be shed.

It is a very prevalent disease in our own country; practically the whole of the adult poor of London suffer from it. It is essentially due to non-use of the teeth, the result of subsisting on a too soft food, which fails adequately to stimulate the flow of blood and lymph in the buccal and peri-odontal membrane, or to elicit that copious flushing of the buccal cavity with the salivary secretions which adequate mastication affords. Vigorous mastication causes the teeth to execute a lively dance in their sockets, and by promoting the normal nutrition of the peri-odontal membrane, thus increases their resistance to pyogenic invasion.

SAPRÆMIA, SEPTICÆMIA, PYÆMIA.

The bacteria which, living on dead organic matter, cause putrefaction are known as *saprophytes* (*sapros*, putrid, rotten), and are described as *non-pathogenic*, because they are unable to grow on or in healthy living tissues, normal vitality being their poison. The bacteria which develop in living tissues are known as *parasites*, and are described as *pathogenic*.

Bacterial Products.—The most important of these are the *toxins*, which are the essential cause of the symptoms of bacterially induced disease.

Sepsis.—This term is generally used in connection with wounds. A wound is said to be in a condition of *sepsis*, or to be *septic*, when it has become inoculated with pathogenic or non-pathogenic bacteria.

Infection is the term applied when pathogenic organisms, having entered the living body, develop therein.

Sapræmia, or Septic Intoxication.

If putrid blood-serum or the fluid of decomposing tissue is carefully *filtered* and injected into an animal, there result rigor, pyrexia, muscular twitchings, vomiting, diarrhœa, and eventually, if the dose is sufficiently large, death from cardiac failure.

On examining the dead animal, the blood is found to be tarry and imperfectly coagulated, but *free from micro-organisms;* the endothelium of the heart and bloodvessels is stained by pigment derived from disintegrated chromocytes; small petechial hæmorrhages are noticed beneath the serous membranes; the lungs are engorged; the liver, spleen, and kidneys are soft, pulpy, and friable; and the intestinal mucous membrane is intensely congested.

The term **Sapræmia** is applied to the constitutional symptoms, similar to those just indicated, resulting from the absorption into the system of toxins generated by non-pathogenic organisms existing in a septic wound. The organisms being non-pathogenic, the poison is not self-multiplying within the body, and its effects are not necessarily fatal, but proportional to the dose absorbed. As found in man, examples are: the pent-up discharges between the flaps of an amputation stump, the decomposed retained matter in the uterus after parturition, and other allied conditions.

Septicæmia, or Septic Infection.

If *unfiltered* putrid fluid is injected into an animal, the result is the setting up of a train of symptoms very similar to those found in sapræmia; but the animal soon dies, even after very small injections, and *large numbers of micro-organisms are found in the blood.*

The term **Septicæmia** is applied to the condition which results from the entrance into the system of pathogenic organisms from a septic wound. The wound may be of the most trifling nature, but if it serves as the point of entrance of pathogenic organisms, these may multiply in the system *ad infinitum*, and this being so, the symptoms are not proportional to the dose absorbed. In man septicæmia most frequently results from punctured, dissecting, and post-

mortem wounds, and from infection during the puerperium. Most cases are due to streptococci.

Pyæmia.

If a putrid fluid, holding in suspension not merely pathogenic micro-organisms, but decomposing solid particles, is injected into an animal, death takes place, and secondary abscesses are then found in the lungs, spleen, kidneys, and brain.

The term **Pyæmia** is applied to a condition similar to the last, in which there occurs, in addition, a passage of septic emboli into the blood-stream, giving rise to scattered abscesses. These emboli are derived from the breaking down of a septic thrombus in a vein, the sequence of events being—

(*a*) Septic phlebitis in connection with a wound.

(*b*) Inoculation of the contained thrombus with pathogenic organisms.

(*c*) The breaking down of the thrombus into emboli.

(*d*) Distribution of the emboli into the circulation.

(*e*) The plugging up of the terminal arterioles of the lungs, spleen, kidneys, etc., by such emboli.

(*f*) The formation of infarcts, in which are reproduced the conditions existing in the original wound (= pyæmic abscesses).

The micro-organisms are the same as those found in septicæmia, streptococci being the most abundant.

Pyæmia was, in pre-Listerian days, a very common cause of death after operations and certain injuries, especially those implicating veins, bones, or joints; now it is but rarely seen.

Post-mortem Changes.

The *veins* leading from the infected wound show suppurative phlebitis and peri-phlebitis, and they contain thrombi in various stages of decomposition and disintegration.

The *lungs* are congested, and scattered throughout their substance are septic infarcts, ranging in size from a pea

to a walnut, and having their bases beneath the pleural surface. In the neighbourhood of the infarcts are patches of broncho-pneumonia. The pleural sacs contain a quantity of a dark-coloured turbid fluid mixed with pus.

The *heart muscle* is flabby, and small abscesses may be seen in its substance. The pericardium may contain fluid similar to that found in the pleura. The interior of both the heart and the aorta is generally deeply stained with pigment derived from broken-down chromocytes.

The *liver*, *spleen*, *kidneys*, and *brain* usually show infarcts similar to those found in the lungs.

The *joints*, particularly those of the knee and shoulder, are often affected, and become filled with a thin purulent liquid.

Abscesses may form in other parts of the body, such as the parotid gland and interior of the eye.

Portal pyæmia, or **suppurative pylephlebitis**, is that form of pyæmia which occurs in connection with ulceration of the gastro-intestinal tract or gall-bladder, or inflammation of the umbilical vein in newly-born infants. Multiple septic infarcts are found scattered throughout the liver, corresponding in situation to the terminal branches of the portal vein.

Summary.

Sapræmia = absorption of toxins of non-pathogenic organisms. Non-self-multiplying in the blood.

Septicæmia = absorption of pathogenic organisms + their toxins. Self-multiplying in the blood.

Pyæmia = absorption of septic emboli + pathogenic organisms + their toxins. Self-multiplying in the blood.

ANIMAL PARASITES.

Classification.

Cestoda, or tape-worms	*Tænia solium.*
	Tænia mediocanellata.
	Tænia echinococcus.
	Bothriocephalus latus.

Nematoda, or thread-worms	*Ascaris lumbricoides.* *Oxyuris vermicularis.* *Tricocephalus dispar.* *Ankylostoma duodenale.* *Trichina spiralis.* *Filaria sanguinis hominis.* *Dracunculus medinensis.*
Trematoda, or fluke-worms	*Schistosomum*, or *Bilharzia hæmatobia.* *Schistosomum cattoi.* *Schistosomum japonicum.*
Protozoa	*Amœba coli.* *Trypanosoma.* *Hæmatozoon malariæ.* *Spirocheta pallida.* *Leishman's body.*

Cestoda (*kestos*, a girdle).

The members of this group have a life-history which is peculiar in that it embraces two distinct stages of existence —the *adult stage*, generally found in one species of animals (the host), and the *embryonic stage*, found usually in another species (the intermediate host).

The adult tape-worm occupies the intestines. It consists of a head, a narrow neck, and a series of flattened segments or *proglottides*.

The head at its widest part is provided with four suckers, by means of which it fastens itself to the intestinal mucous membrane of the host, and anteriorly it is prolonged into a *rostellum* or proboscis surrounded by two rows of hooklets.

Commencing at the anterior part of the body and running backwards along each side are two longitudinal tubes—the *water vascular system*. There is no alimentary canal.

Each proglottis is bisexual, the respective sexual ducts opening at the genital papilla, which is placed at one edge of each proglottis, the papillæ being at alternate sides of succeeding segments.

The *testes* consist of small vesicles, the ducts of which unite into a vas deferens, which enters the penis.

The *uterus* is branched, having a central canal with lateral diverticula, and being connected at one end with *two ovaries* by means of two oviducts, and at the other

end with a vagina. The spermatozoa travel from the penis, enter the vagina at the genital pore, and then fertilize the ova. The distal proglottides, holding the embryos, become detached, and escape from the intestines with the fæces.

The proglottis then decomposes and liberates the embryos, which are each provided with six hooks and surrounded by a capsule. If the embryos are now swallowed by another animal (*the intermediate host*), their capsules are dissolved by its digestive juices, and the embryos escape into the alimentary canal of the new host. They then bore their way through its walls, and finally settle in the viscera or the muscles. After this the further development of the embryo is as follows: The hooklets disappear, and a cavity develops at the opposite end, in the interior of which an immature head (*scolex*) appears, the whole organism being afterwards enclosed by a fibrous capsule formed by condensation of the surrounding connective tissue. This intermediate stage is known as the *Cysticercus cellulosæ*, or bladder-worm. Should the flesh of the animal harbouring the *Cysticercus cellulosæ* now be eaten by another animal, the head of the cysticercus becomes everted and losing its bladder-like appendage, fastens itself to the intestine by means of its four suckers and develops proglottides from its opposite end.

Hydatid Cyst.—The intermediate stage of the *Tænia echinococcus* is known as the hydatid. The embryos, provided with their six hooks, enter the alimentary canal of some animal — say, man — and their capsules being dissolved by the digestive juices, they are set free. They then bore their way into the tributaries of the portal vein, and so reach the liver or other organs, where they come to rest.

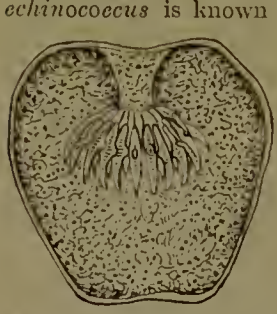


Fig. 8.—Brood Capsule.

Each embryo now loses its hooklets and is converted into a cyst, the walls of which are composed of concentric lamina lined by granular cells—the *germinal membrane*—and filled with a non-albuminous

fluid rich in sodium chloride and containing the hooklets, which are of great diagnostic value. Within the cyst are *brood capsules;* these are small vesicles which, originating from the germinal membrane, contain immature heads (*scolices*) crowned with hooklets, and are analogous to the *Cysticercus cellulosæ* of the other tape-worms.

The entire hydatid cyst is surrounded by an adventitious capsule of fibrous tissue.

TABLE OF CHIEF POINTS.

Name.	Tæuia solium.	Tænia mediocanellata.	Tænia echinococcus.	Bothriocephalus latus.
Length ...	10 feet	15 feet	$\frac{1}{4}$ inch	20 feet
Proglottides	800	1,000	3, exclusive of head	3,500
Head ...	$\frac{1}{24}$ inch	$\frac{1}{12}$ inch	$\frac{1}{30}$ inch	$\frac{1}{10}$ inch
Rostellum...	Present	Absent	Present	Absent
Hooklets ...	26	Absent	Present	Absent
Suckers ...	4	4	4	2
Intermediate host ...	Pig	Ox	Man and sheep	Sturgeon, pike, trout

N.B.—*Average* length and number of proglottides given.

Nematoda (*nema*, a thread).

These are slender, elongated worms tapering at the extremities. Each has an alimentary canal, with mouth and anus. The sexes are distinct, the female being the larger. A few typical members of the class alone need be described.

Ankylostoma Duodenale. — The female is about $\frac{1}{2}$ inch in length, the male slightly shorter. The mouth is furnished with teeth, by which the worm fastens itself to the duodenal mucous membrane of the host. The egg

is enclosed within a thin transparent capsule, and is voided with the fæces. It then matures in damp earth, the embryos invading the body of the new host, probably by penetrating the skin, generally that of the feet or legs.

From the skin they enter the blood, ultimately reaching the lungs. Up to this time they retain their original size, but once in the air-passages of the lungs their growth is rapid. They then travel up from the air-vesicles into the bronchi, trachea, and glottis, and emerge into the œsophagus, whence they pass into the duodenum, in which place they attain maturity.

These parasites, in virtue of their leech-like habits, suck a great quantity of blood from the duodenal mucous membrane, causing a serious form of anæmia (*coolie anæmia*), which is associated with a great increase in the eosinophile leucocytes in the blood. The worm recently made its appearance amongst the miners engaged in the Dalcoath tin-mine in Cornwall. It is common in Egypt, Brazil, Italy, and other hot countries.

Trichina Spiralis.—The female is about $\frac{1}{8}$ inch long, and the male about $\frac{1}{12}$ inch. The mature worm is found in the intestines of man and other animals; the immature form is found in the muscles. The ova are hatched into embryos in the uterus, *the young being born in the free state.* The life-history of this parasite is as follows: When infected pork, *e.g.*, is eaten, the capsules containing the embryos are dissolved in the stomach by the digestive juices, and the liberated young worms pass into the intestines. Here in the course of a few days they attain maturity and pair, and in about a week after fertilization the young begin to be born, in the next few weeks each female giving birth to a thousand or more. The embryos, now free in the intestines, proceed to migrate, entering the blood and lymph; carried by these fluids to the striated muscles, they bore their way through the sarcolemma, coil themselves up in the interior of the fibre, and become encysted, in this position undergoing no further development until the infected flesh is eaten by a new host. After a time the cyst wall may calcify. The cysts are visible to the naked eye as minute white specks, first observed by Sir James Paget, when a student in the dissecting-room of St. Bartholomew's Hospital.

They have been found in all striated muscle except that of the heart.

The disease is conveyed to man by the ingestion of imperfectly cooked trichinosed pork; the pig is usually infected by eating trichinosed rats.

Filaria Sanguinis Hominis.—The adult form of this worm is known as the *Filaria bancrofti*, and the embryonic form as the *Filaria nocturna*.

Filaria bancrofti.—This form is confined to the lymphatics. The female is about 3½ inches long, the male only about half this size.

Reproduction is viviparous, the female discharging her embryos into the lymph, by which they are carried into the blood-stream by way of the thoracic duct.

Filaria nocturna.—The snake-like embryo is about $\frac{1}{90}$ of an inch long, its breadth about the diameter of a red blood-corpuscle. The head is provided with a short spine and a circlet of hooked lips.

The organism is imprisoned within a long loose sac, inside which it can be seen to wriggle, but from which it is powerless to escape so long as it remains in its human host.

The embryos are present in the surface bloodvessels during sleeping hours only—whence the name *F. nocturna;* when the patient awakes they gradually retire to the lungs and larger bloodvessels. The cause of this remarkable periodicity is unknown. If a filarial patient changes his hours of sleep from night to day, the periodicity correspondingly changes.

As these filariæ cannot further develop in the human host, they probably soon die unless they are removed to an intermediate host. This latter is a species of mosquito (*Culex fastigans*), which swallows the filaria when sucking human blood. In the mosquito's stomach the embryo escapes from the sac which has hitherto enclosed it, and bores its way through to the thoracic muscles where it comes to rest. By about four weeks' time it has grown considerably, and then, resuming its travels, it reaches the proboscis, and returns to another human host when the insect stings. It now passes to the lymphatics, where it matures into the *Filaria bancrofti.* The sexes then come together, and the young are born.

Filariasis.—In the large majority of cases the presence of filariæ in the human body gives rise to no obvious symptoms. Occasionally, however, the mature worm may block the lymphatics, or possibly the female discharges, instead of embryos, unhatched ova which are large enough to obstruct the lymph-stream. When this happens any of the following tropical diseases may result:—

Chyluria, probably due to ruptured lymphatics in the urinary tract, the urine becoming milky in appearance and coagulating into a jelly after standing.

Lymph scrotum, characterized by dilated and varicose lymphatics in the scrotum, which sometimes burst.

Elephantiasis Arabum, characterized by hypertrophy of the tissues, the result of blocked lymphatics. It is most commonly met with in the legs and genitals. Enormous tumours may thus form, the scrotum, for instance, alone having been known to weigh as much as 100 pounds.

Varicose lymphatic glands, giving rise to soft, painless tumours, over which the skin can be moved.

Abscesses, from the irritation caused by blocked lymphatics or by dead filariæ.

In addition to the *Filaria bancrofti* and its embryonic form, *Filaria nocturna*, which are found all over the tropics, there are at least three other species found in the tropics—viz., *Filaria diurna* (West Africa), *Filaria perstans* (Africa and Demerara), and *Filaria demarquai* (West Indies and Demerara).

Trematoda.

The only member of this group at all common in man is the *Bilharzia hæmatobia*. The parasite is found in Natal, the Transvaal, Egypt, Madagascar, and the West Indies (particularly Porto Rico).

The female worm is about 1 inch long, the male about ½ inch, and they inhabit the portal vein and its tributaries and the vesical veins.

The ventral surface of the male is concave, and during copulation the lateral borders become infolded so as to enclose the female in a 'gynæcophoric canal.' The ova are shaped like melon-seeds, being provided at the pointed end with a spine, by means of which they work their way through the walls of the small veins and emerge into the

interior of the rectum or bladder, whence they are discharged with the fæces and urine. A good deal of oozing of blood from the mucous surfaces may be caused by the migration.

The ova cannot mature whilst in the blood or urine, but if placed in water, or if the urine be diluted with water, the capsules then burst and the ciliated embryos are set free.

As regards the intermediate host nothing is known; analogy with the history of the other nematodes would suggest that the embryo enters some fresh-water animal, in whose body it undergoes a further developmental change. Infection in man is probably through drinking-water, although it is thought by some investigators that the embryos enter the urethra or anus during the act of bathing.

The effect of the parasite is to cause *endemic hæmaturia*, as also the passage of blood from the rectum. Condylomata may develop both inside and outside the anus, and for this reason the case may be diagnosed as syphilis.

The period of incubation which elapses between infection and the appearance of ova in the urine extends, probably, to over four months.

Protozoa.

The term *Protozoa* is applied to the lowest group of the animal kingdom, which is sharply distinguished from other groups (*Metazoa*) by the fact that its members are simple undifferentiated masses of protoplasm.

Amœba coli is found in the dejecta and the ulcers of the diseased bowel in Asiatic dysentery, and in the walls of a tropical abscess of the liver.

The organism measures 30 to 40 μ in diameter, and consists of an outer translucent part, the *ectosarc*, and an inner granular part, the *endosarc*. It is colourless, throws out pseudopodia, is actively motile, and in its general characters resembles the ordinary amœba. Reproduction is by fission.

Trypanosomata are minute protozoal organisms shaped like an elongated spindle, with a long lash or flagellum at one end, and a delicate fin-like swimming

membrane running from the attachment of the flagellum to the other end of the spindle. For the most part they are about the length, exclusive of the flagellum, of the diameter of a red corpuscle. They swim very actively in the blood-plasma, with a wriggling screw-like movement, the flagellum being usually in front' (Manson).

One species, the *Trypanosoma gambiense*, is probably the cause of that scourge of Africa, the *sleeping sickness*, as it is found in the blood, cerebro-spinal fluid, and lymphatic glands of patients suffering from it.

(In sleeping sickness there is a well-marked cerebro-spinal meningitis.)

Another species, the *Trypanosoma brucei*, causes the tsetse-fly disease of horses, dogs, sheep, and the large game of Africa, the fly acting as the intermediary which carries the parasite from one mammal to another.

A third species, the *Trypanosoma lewisi*, infests the rat.

Hæmatozoon Malariæ.—Malarial fevers are caused by the presence in the blood of a small protozoon—the *Hæmatozoon malariæ*. This parasite has two cycles of existence, one passed in man, the other in the mosquito. Into the human host the organism is introduced by the bite of the mosquito. Its habitat is then the interior of the red blood-corpuscles, where it multiplies asexually by simple division. In addition to this method of asexual reproduction, the parasite also produces crescent-shaped sexual forms, which under ordinary circumstances perish in the blood (being probably engulfed by the phagocytes); but if they are transferred into the body of the mosquito, they undergo further development there. This transference is effected when the insect bites a man with these forms in his blood, after which sexual reproduction takes place in the stomach of the mosquito.

In the proboscis of the mosquito there are two separate tubes, one *up* which blood is sucked, the other *down* which the saliva is injected.

Characteristics of the Mosquito.

Of the three to four hundred described species of mosquito, only a limited number are malaria-carriers, and these belong to the sub-family *Anophelina*.

In common with other insects the mosquito passes through the following stages of development: The adult female lays her eggs in *still* water. In the course of from two to four days these are hatched into *larvæ*, which in about ten days' time are transformed into the *pupæ*, these, two days later, becoming full-grown insects, or *imagos*. They then burst their pupa-cases, and fly away from the water.

The female anopheles alone is the blood-sucker.

The vitality and growth of the mosquito are favoured by warmth, and retarded or altogether arrested by cold.

The malarial parasite, once introduced into the blood of man, may persist for months, sometimes for a year or two. After this it dies out, unless reinfection by the mosquito takes place. Whilst in the blood it lives entirely at the expense of the red corpuscles of its host.

The Human Cycle.—At the time of infection by the bite of the mosquito a minute rod-shaped body (18) is introduced into the blood of the human host. This rod, or *amœbula*, at once enters a red blood-corpuscle (1), in the interior of which it develops asexually in the following manner: It first becomes a small spherical unicellular mass of protoplasm (2, *schizont*), exhibiting amœboid movement and occupying but a small part of the corpuscle. Gradually it grows larger and larger (3) until it occupies nearly the whole corpuscle, the hæmoglobin of which is converted into granules of pigment, which ultimately collect into clumps. The parasite now undergoes segmentation, arranging itself in a cluster of little spherules, forming what is known as the *rosette body* (4). This soon breaks up into separate parts (5, *merozoites*), and by the end of a definite time—twenty-four, forty-eight, or seventy-two hours—the corpuscle ruptures and liberates these into the plasma (6). Each merozoite then invades a fresh red corpuscle (1), in which it repeats the same cycle of development.

This asexual process of multiplication by simple division is known as *schizogony*.

The setting free of the merozoites into the plasma coincides in time with the onset of the febrile attack, and it is probable that a fever-producing poison is also liberated when the corpuscle bursts.

A parasite which matures every twenty-four hours produces *Quotidian* fever, one which matures every forty-

eight hours *Tertian* fever, and one maturing every seventy-two hours *Quartan* fever.

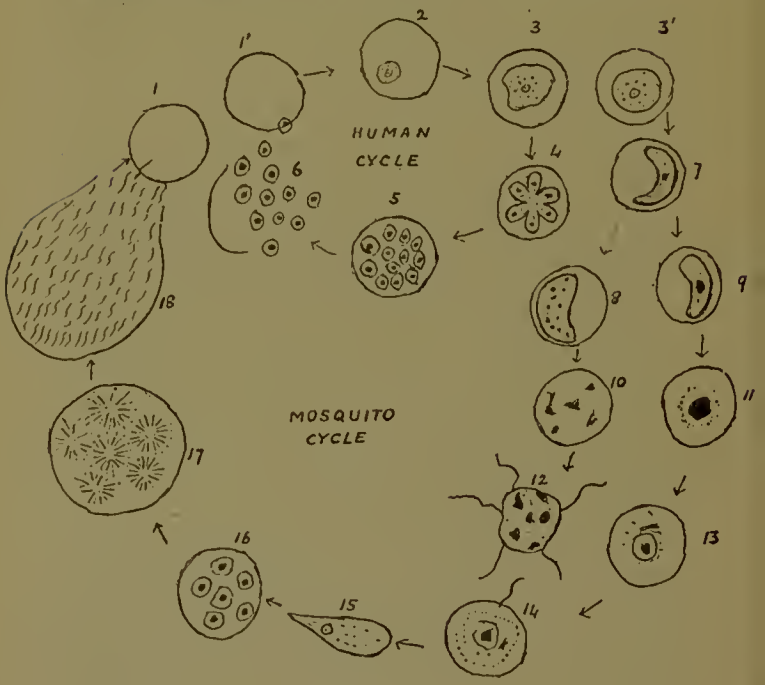


FIG. 9.

1. Red corpuscle with sporozoite entering. 1'. Red corpuscle with merozoite entering. 2, 3. Amœbula developing within red corpuscle (schizont). 4. Rosette body. 5. Formation of merozoites. 6. Liberation of merozoites into plasma by bursting of red corpuscle. 3'. Amœbula, which becomes (7) crescent body. 8. Male crescent. 9. Female crescent. 10. Male gametocyte. 11. Female gametocyte. 12. Formation of microgametes in male gametocyte. 13. Formation of macrogamete in female gametocyte. 14. Fertilization of macrogamete of female gametocyte by a microgameto of the male gametocyte, which now becomes a zygote. 15. Ookinet. 16. Oocyst. 17. Development of sporoblasts. 18. Liberation of sporozoites. (*Vide* 'Malaria in India,' by Captain James, I.M.S.)

The Mosquito Cycle.—In addition to the above asexual multiplication, some of the parasites in the red corpuscles develop (as before explained) into crescent-shaped sexual forms (7).

The crescents contain pigment, and are of two distinct kinds: (*a*) The *female crescent* (9), a long and narrow crescent, round the centre of which the pigment is arranged in a circle; (*b*) the *male crescent* (8), a shorter and thicker crescent, throughout which the pigment is scattered irregularly.

Each of these bodies, (*a*) and (*b*), remains enclosed within the thin shell of its respective red blood-corpuscle, and if left in the blood of man undergoes no further development. Should, however, a mosquito bite a person in whose blood these crescents exist, they are then conveyed into the insect's stomach, and there, escaping from the red blood-corpuscles, become free.

The crescents now become spherical, and are known as the female (11) and male (10) *gametocytes* respectively. From the outside of the male gametocyte (12) whip-like filaments (*microgametes*) now protrude, and, becoming detached, swim about in the stomach of the mosquito until, meeting a female gametocyte (13), one of them fertilizes the large cell (*macrogamete*) contained in it (14), and gives rise to a *zygote*.

The zygote, at first spherical, becomes ovoid with a pointed end (*ookinet*, 15) and, acquiring powers of locomotion, burrows through the epithelial lining of the stomach, and comes to rest between the epithelial and the muscular layers.

Here it forms a capsule round itself, becomes spherical, and begins to grow (*oocyst*, 16), till by the end of from ten to fourteen days it has attained a comparatively large size. 'During this time the contents have become converted into a number of rounded masses (*sporoblasts*, 17), each of which, when the process of subdivision is completed, becomes covered with a pile of thickly set, minute, elongated, spindle-shaped rods (*sporozoites*, 18), arranged like the spines on a hedgehog' (Manson). Finally, the capsule ruptures, and the sporozoites, escaping into the lymphatics on the outer surface of the stomach, enter the circulation, and are ultimately conveyed to the salivary

gland. When the mosquito bites a man, the sporozoites travel down the proboscis with the salivary or poison fluid, and are injected into their human host (1).

Summary.

The *female gametocyte* encloses a single cell, called the *macrogamete*, which is the homologue of the ovum.

The *male gametocyte* develops upon its exterior whip-like processes, called *microgametes*, which are the homologue of the spermatozoa.

One of these microgametes fertilizes a macrogamete, the result being a *zygote*.

The zygote, when it has acquired powers of locomotion, is termed an *ookinet*. The encysted ookinet in the stomach wall is called an *ooeyst*.

In the oocyst are developed the *sporoblasts*, and from these finally are formed the *sporozoites*.

Leishman's bodies (or **Leishman-Donovan**) are found in the spleen and bone-marrow of tropical splenomegaly, or *kala-azar*. Each is ovoid in outline, with a large deeply staining nucleus, and a tiny rod-shaped, still more deeply staining nucleolus.

The **Spirochæta pallida** is described under Syphilis.

IMMUNITY.

Life has been defined as a continual struggle against death. Hosts of invisible foes (bacteria), ever ready for the attack, encompass the living organism, and were it not provided with suitable defensive mechanisms against them, existence for it would be impossible. Such defences consist of means of preventing the entrance of bacteria into the organism, such as is afforded by healthy skin and mucous membranes (*first line of defence*), means of destroying them after their entrance and of neutralizing the deadly poisons to which they give rise (*second line of defence*).

The human body, the organism with which we are here concerned, may thus be compared to a fort perpetually invested by the enemy's battalions, and it is only by

keeping in a constant state of preparedness that it can successfully resist their attack.

Susceptibility.

Natural Susceptibility.—If a mouse is inoculated at the tip of its tail with anthrax and the tail is amputated, even though it be within one minute of the inoculation, the animal will succumb to anthrax—a striking instance of natural susceptibility.

Man is similarly susceptible to certain bacteriogenic diseases, such as hydrophobia and syphilis.

Acquired Susceptibility.—The hen is naturally insusceptible to anthrax; when its feet are immersed in cold water, however, it becomes susceptible, and experiments have proved that not only cold, but hunger, thirst, improper feeding, fatigue, and loss of blood, all tend to increase susceptibility to bacteriogenic diseases. White rats, for example, which are ordinarily insusceptible to anthrax, become susceptible after fatigue, or when fed upon a purely vegetable diet. Again, while healthy swine do not contract glanders, young and debilitated pigs may sometimes be affected with it.

Immunity.

By immunity is meant non-susceptibility to bacteriogenic disease. Rinderpest is essentially a disease of ruminants; horses never contract it. Tuberculosis, though common in cows and pigs, is very rare in horses, asses, sheep, goats, and dogs. Again, Algerian sheep are immune against anthrax, although ordinary sheep are susceptible to this disease.

Immunity, like susceptibility, is a *relative* term. With few exceptions, no animal which has been made the subject of observation possesses absolute immunity against any given microbial disease under every possible circumstance.

After infection, the organism brings into action certain defensive mechanisms which have for their object—

(*a*) The destruction of the invading bacteria (= *antibacterial*); and

(*b*) The neutralization of the poisons engendered by the bacteria (= *antitoxic*).

In connection with the bacteriogenic diseases, two main facts have to be borne in mind:

(1) The entrance of the bacteria into the body, and their subsequent multiplication therein.

(2) The production by them of poisons, to the action of which on the tissues all their morbid effects are due.

These poisons consist of the bacterial 'toxins,' substances formed in and by the bacterial protoplasm, and of poisons generated by the digestive action of the bacteria on the fluids and tissues of the body.

Bacteria, *i.e.*, exert their poisonous action not only through the agency of their toxins, but also by a digestive action quite distinct from that of their toxins, leading to the formation in the tissues of other poisonous substances, such as albumoses, peptones, organic acids (formic, acetic, butyric), and aromatic compounds (indol, phenol, mercaptan).

Toxins.

The bacterial toxins (*toxikon*, poison) are poisonous substances allied to proteids, and, like them, possessing a highly complex composition. Just as certain plants possess their special alkaloids (strychnine, morphine, aconitine, etc.), so each species of bacteria elaborates its own particular products, some of which may be useful to their host, some innocuous, and some harmful. It is to these latter poisonous products that Brieger gave the name of *toxins*.

It is to be understood that in speaking of the toxins of a particular bacterium it is solutions of them that are meant, no toxin having, as yet, been isolated and analysed as the vegetable alkaloids have been.

It is probable that there are two kinds of bacterial toxins:

(*a*) Those confined to the interior of the living bacteria, and only liberated on the death of the microbes (*intracellular*, or endo-toxins); and

(*b*) Those yielded by the living bacteria to the medium outside them (*extra-cellular*, or exo-toxins).

(*a*) *Intra-cellular Toxins.*—In this group, which includes the toxins of the greater number of bacteriogenic

diseases, amongst others those of tubercle, enteric fever, cholera, and pyæmia, the toxin is intimately bound up with the protoplasm of the bacteria, only being liberated when these degenerate or die. It is found, in the particular diseases just referred to, that if the bacteria causing them are grown in a suitable culture medium no toxin separates out by filtration through porcelain, whereas if the bacteria are frozen at the lowest of temperatures and then crushed, the result is a highly toxic substance.

(*b*) *Extra-cellular Toxins.*—In this group, which includes the toxins of diphtheria and tetanus, the toxin appears to be of the nature of an excretion. If, for example, the diphtheria or the tetanus bacillus is grown in a suitable medium *soluble toxins are found to pass out into the medium, from which they can be separated by filtration through porcelain*, the inference being that the bacilli in question excrete them (unless we suppose that they produce them by promoting some change in the external medium).

Some species of bacteria produce both intra-cellular and extra-cellular toxins—*e.g.*, tubercle bacillus (probably).

According to Ehrlich, diphtheritic sorum contains three distinct substances—the *toxin proper*, the *toxoid*, and the *toxone*.

The toxin is the poisonous element, and can combine with the antitoxin.

As the sorum becomes older it loses its toxic property but retains its power of combining with the antitoxin; this is due to its conversion into toxoid.

The toxone also possesses the power of combining with the antitoxin, but, unlike the toxoid, it is poisonous, though only in a limited degree—*e.g.*, it can produce post-diphtheritic paralysis. Unlike the toxoid, too, it is not a derivative of the toxin but results from the direct action of the microbe.

Action of Toxins.—They appear to unite with the protoplasm of the tissues. In many of their properties, however, they resemble ferments. Thus:

They are destroyed by a temperature of from 140° to 212° F. They are precipitated by alcohol; they are unaffected by chloroform and ether. They can be swallowed with impunity. They do not act until after a latent period. They act irrespectively of the quantity employed—*i.e.*, an infinitesimal dose is effective; *e.g.*,

$\frac{1}{1000}$ gramme of tetano-toxin will kill a horse 600,000,000 times its own weight.

Fate of Toxins.—Ultimately toxins are partly excreted as such (chiefly by the kidneys and liver), partly burnt up in the tissues, and partly neutralized by antitoxin. Resistance to bacteriogenic disease varies with many circumstances, amongst the most important being—

1. *Species.*—Cholera and enteric fever, *e.g.*, are confined to the human being.

2. *Racial and Individual Peculiarities.*—Thus, certain races do not contract yellow fever or enteric; again, certain individuals never contract pneumonia.

3. *Age.*—Adults rarely contract whooping-cough, or old people enteric.

4. *Altered Vitality.*—Examples illustrative of the influence of this factor have already been given.

Immunity may be—

A. Natural, or
B. Acquired.

A. **Natural Immunity.**—This in some cases has been achieved by natural selection. In this way a race may become completely or partially immune as regards a disease to which its ancestors were highly susceptible. It is probable, however, that the susceptibility of a species to bacterial infection essentially results from *the bacterial parasite having acquired the power to infect;* and when a species is immune as regards a particular bacterium, it may be, and in all probability generally is, because this latter has not acquired the power of establishing a lodgment in that species.

For examples of natural immunity, see p. 155.

B. **Acquired Immunity.**—Of this there are two chief kinds:

(*a*) Active.
(*b*) Passive.

(*a*) *Active Immunity.*—Examples of this are—

1. Immunity due to a previous attack of an infectious disease—*e.g.*, measles, scarlatina, mumps.

2. Immunity due to inoculation with small doses of the specific *virus* of a micro-organism that has been

passed through the body of another animal, as in the case of vaccination for small-pox.

3. Immunity due to repeated inoculations with sub-lethal doses of *living micro-organisms*, which in course of time produce an immunizing substance in the blood, so that the animal can ultimately tolerate a dose which would at first have been fatal, as in the case of Pasteur's method for fowl cholera (seldom now employed).

4. Immunity arising from inoculation with the serum of an artificially immunized animal—*e.g.*, anti-diphtheritic serum.

(*b*) *Passive Immunity.*—If the blood-serum of an animal rendered immune against a particular disease—*e.g.*, diphtheria—by any of the above methods is injected into a second susceptible animal, this animal also becomes immune against that disease. In such cases the process of immunization is *passive* so far as the second animal is concerned. An infant fed at the breast is less liable to contract disease than one brought up by hand, one reason for this being that it derives immunizing substances from its mother's milk, and in this way is rendered passively immune.

Symbiosis.

Symbiosis, or mixed infection, has a marked influence on the course of bacteriogenic disease. For example, the presence of staphylococci and streptococci in the fauces augments the virulence of the bacillus of diphtheria. Again, without the presence of an aerobic organism, such as the *Staphylococcus pyogenes*, the bacillus of tetanus cannot develop in a wound.

Mixed infection also occurs to a large extent in respiratory and alimentary diseases and profoundly influences their course.

NATURE'S SECOND LINE OF DEFENCE.

This resolves itself into :

(*a*) Substances which act as antidotes to the bacterial toxins ; and

(*b*) Those which act on the bacteria themselves (bacteriocides, bacteriolysins, agglutinins, opsonins, and phagocytes).

(*a*) Action on Bacterial Toxins.

The substances here concerned are possibly of several kinds, the best understood being the *antitoxins—i.e.*, substances which, circulating in the blood of an infected animal, combine with the toxins and thus neutralize their action. Such substances may be normally present in the blood, or they may be generated in it by adaptive reaction.

If, for example, a horse is injected with progressively increasing sub-lethal doses of diphtheritic toxin, the animal acquires immunity against that toxin; and if its blood-serum, thus modified, is injected into a patient suffering from an attack of diphtheria, he may thereby be enabled to recover.

That the neutralizing substance acts upon the bacterial products, and not upon the bacteria themselves, is proved by the fact that *the bacilli of diphtheria will grow readily in diphtheria antitoxin.*

Ehrlich's Theory of Antitoxin Formation.

Bacterial toxins are allied to proteids, and as such possess a highly complex chemical composition, in contradistinction to the ordinary chemical poisons, such as the vegetable alkaloids—*e.g.*, strychnine and prussic acid. These two classes of poisons further differ as regards their chemical action on the tissues, the former entering into more intimate chemical union with them than the latter—so much so that, while it is impossible to recover a bacterial toxin, such as that of tetanus, from the tissues after death, it is quite possible to recover such poisons as strychnine and prussic acid. This, according to Ehrlich, is because the former class of poisons enter into firm chemical union with the living protoplasm, being actually built up into or assimilated by it, while the latter unite with the fatty and other substances entangled in the protoplasmic network rather than with the actual protoplasm itself.

Ehrlich assumes that the molecules of which protoplasm is constituted consist of a central nucleus furnished with numerous side-chains or receptors, adapted to unite with, and thus assimilate, the various food-stuffs circulating in the tissue plasma. Now, when toxins are present they, being, as we have seen, allied to certain food-stuffs, are, as it were, mistaken by the tissues for them, and are caught up by receptors specially adapted to receive them, and are thus assimilated by the protoplasm, the vitality of which is in consequence impaired. It is assumed that under the stimulus of this morbid assimilation the protoplasm produces an

abundance of such specific receptors, and that these, becoming detached, constitute a circulatory antitoxin, which, by uniting with the toxin, neutralizes it, and thus protects the living protoplasm from its action. In this way life tends to be prolonged until the organism has had time to destroy the bacteria which are the source of the toxins.

A blood-serum which possesses immunizing properties that can be utilized to prevent and cure disease is known as an *antiserum*.

Some antisera, such as the anti-diphtherial and the anti-tetanus sera, are antitoxic; others, such as the anti-streptococcal serum, are anti-bacterial.

The mortality from diphtheria in the hospitals of the Metropolitan Asylums Board (London) has fallen from above 30 per cent. to less than 10 per cent. since the introduction of the antitoxin treatment of this disease.

In the treatment of tetanus the antitoxin is of little practical value, because the tetano-toxin rapidly disappears from the blood and travels along the axis cylinders of the nerves to the central nervous system, with the elements of which it is incorporated, thus becoming inaccessible to the action of the injected antitoxin.

(*b*) Action on Bacteria.

The agents here concerned are the bacteriocides, bacteriolysins, agglutinins, opsonins, and phagocytes.

Bacteriocides (*cida*, a slayer).

Freshly drawn-off healthy blood-serum is destructive to a large number of micro-organisms. In course of time, however, this property is lost, and the blood then becomes —like all albuminous fluids—a highly favourable culture medium.

It is obvious, therefore, that substances normally exist in the living blood capable of killing invading bacteria. These have been termed *bacteriocides* (= alexins of Buchner).

Bacteriolysins (*lyo*, dissolve).

Pfeiffer's Phenomenon.—If a guinea-pig is immunized against cholera by injecting it with small and gradually increasing quantities of the cholera vibrios, vibrios sub-

sequently injected into the peritoneal cavity of such an animal first become motionless, then die, and ultimately disappear. Seeing that few, if any, leucocytes are present in the peritoneal cavity, Pfeiffer regards the substance causing the phenomenon as an excretion from the endothelium lining the peritoneum, and inasmuch as it dissolves the organisms, it is a *bacteriolysin*. Outside the body, the blood-serum of a highly immune guinea-pig has similar bacteriolytic properties.

Hæmolysins.—If the chromocytes of one species of mammal, *e.g.*, the horse, are introduced into the body of another species of mammal, *e.g.*, the dog, the latter animal elaborates a serum capable of dissolving the chromocytes of horses in general. Such a serum is said to contain hæmolysins. The serum may in a similar way be made to acquire the property of dissolving other cells, such as those of the kidney, liver, and testes, and such sera are said to contain **cytolysins** (*kytos*, a cell; *lyo*, dissolve), of which nephro-, hepato-, and spermato-lysins are examples.

Agglutinins.

If the diluted blood (1 in 20, 1 in 50, or even 1 in 1,000) of a typhoid patient is added to a broth culture of the *Bacillus typhosus*, the microbes lose their motility and become massed into clumps, an effect not to be observed if the blood of a person not suffering from the disease is used. This phenomenon is known as *agglutination*, and is supposed to be due to the development in the blood of a substance—*agglutinin*—which, by softening the outer membrane of the bacilli, causes them to become glued together. As a test applied in the diagnosis of typhoid fever, the phenomenon is known as *Widal's reaction*.

Agglutination may also be observed in Malta fever, and other organisms give the same reaction (*e.g.*, *Bacillus coli*, tubercle bacillus, Gaertner's bacillus), but in all these cases the serum requires to be much less diluted for the test than in the case of typhoid fever.

The Elimination of Agglutinins in the Urine of Patients suffering from Typhoid Fever.—Dr. Heinrich von Hoesslin, of Munich, has published in the *Münchener Medizinische Wochen-*

schrift of April 30 some interesting clinical and experimental observations to determine whether the agglutinating substances in the blood are demonstrable in the urine. At the outset it was important to differentiate between patients in whom the kidneys were normal and those with albuminuria. He found that in the former group—*i.e.*, patients passing urine free from protein—no agglutination was obtained with the urine, whether the agglutinating power of the blood were high or low. On the other hand, in three cases of typhoid fever with acute hæmorrhagic nephritis the urine was found to have distinct agglutinating properties, the intensity of which depended upon the agglutinating power of the blood and the amount of protein in the urine. Similar results were obtained in cases without actual nephritis, but with febrile albuminuria. Here the agglutinating powers were less marked than in the cases with nephritis, but were quite easy to demonstrate. These observations were experimentally confirmed in rabbits. Dr. von Hoesslin concludes that the normal kidneys are impermeable to the agglutinins; that these substances can, however, be eliminated in company with proteins in the urine when the kidneys are damaged, and that the amount of agglutinins so secreted is more or less proportional to that of the protein. It has already been shown by Pick that the agglutinins are of protein-like character, and that they can be precipitated together with the eu-globulin fraction of the blood proteins. Many views have been put forward as to the origin of the agglutinins; the spleen, the lymphatic glands, and the bone marrow have all had this function attributed to them, while Gruber is of opinion that the leucocytes are also concerned in their production; but as to the channels by which they are eliminated little or nothing has been hitherto known, except that they are not found in the ordinary secretions and excretions, with the exception of the milk during lactation, in which, according to Stäubli, they may be present in greater quantity than in the serum. They have also been found in the serum of blisters, in pericardial and pleural exudates, and in the fluid of œdema. Dr. von Hoesslin also finds that an inflammatory process increases the amount of the agglutinins in any exudate—*e.g.*, in the cerebro-spinal fluid of a case of meningitis complicating typhoid fever the amount of these substances present was found to be markedly increased (*Lancet*, August 24, 1907).

Opsonins ('Feast-preparers').

As the subject of opsonins is intimately related to that of phagocytosis, it is necessary to have a clear idea of what is meant by this latter process.

So far as pathology is concerned, phagocytosis deals with the ingestion of bacteria, and the process resolves itself into a battle between phagocyte and parasite, in

which either may prove victorious. 'Sometimes the phagocytes devour at one swoop whole masses of the organisms' (Metchnikoff).

The phagocyte, as it were, 'recognizes in the microbe a foe to the organism; scents it from afar; hunts, seizes, and digests it; and then, its duty done, its mission in life fulfilled, it withdraws its pseudopodia and dies contentedly' (Adami).

If the invading bacteria are very virulent, they may kill the phagoeytes, or if their spores have been taken up by the phagoeytes, these may develop within the phagocytes and destroy them.

The bacteria engulfed by the phagoeytes either undergo intra-cellular digestion or are destroyed by a ehemical poison, probably related to nucleic aeid and secreted by the eell nueleus (Kossel).

Metehnikoff distinguishes between two forms of phagocytes:

(*a*) The *microphages*, or polymorphonuclears, whieh are mainly concerned in the destruction of bacteria; and

(*b*) The *macrophages* (ineluding the large lymphocytes, the conneetive-tissue eells, endothelial eells, and eertain eells of the splenie pulp and bone marrow), which are mainly eoncerned in the removal of dead cells and tissues.

Chemiotaxis.—The migration of the leucocytes is explained on the hypothesis of chemiotaxis. 'The phagocytes possess a kind of sense of taste, or chemiotaxis, which enables them to distinguish the chemical composition of the substances with which they come into contact' (Metchnikoff).

In the case of the less virulent infections, the invading microbes secrete a substance which attracts the phagocytes (=*positive chemiotaxis*), thus enabling the latter to ingest and destroy them.

In the case of the more virulent infections, such as the acute septicæmias, the microbes secrete a substance which repels the phagocytes (=*negative chemiotaxis*), thus enabling the invaders to multiply without hindrance.

'But although a chemical attraction may be regarded as one of the important influences determining emigration there are other stimuli which excite leucocyte activity. Like other living cells, leucocytes are sensitive to physical stimuli of various kinds. This physiotactic activity includes the reaction to light, heat, electricity, and to tactile stimuli. And the facts which are known as to the effects of other kinds of stimuli on

some unicellular organisms make it probable that there are other less known agencies to which they are sensitive' (Professor Greenfield).

Elias Metchnikoff and his school believe that the phagocytes are the essential agents in the destruction of bacteria, and that the blood-plasma takes little or no part in the process; also that the various 'lysins' present in the blood originate from the leucocytes. '*It is the phagocyte*,' he says, '*which delivers us from our enemies*.'

Wright and Douglas, while accepting the main thesis of Metchnikoff—viz., that the final destruction of the bacteria is brought about by the phagocytes—contend that these latter are incapable of ingesting bacteria unless they have been acted on by a substance present in the plasma, for they find that if leucocytes are separated from the blood and washed they possess little or no power of phagocytosis, but that if to the washed leucocyte blood-serum is added, phagocytosis at once takes place, thus showing that the serum contains a something which is essential to that process. Metchnikoff, while admitting this, affirms that this something is derived from the leucocytes: 'Either the absorption of the microbes may be effected without the help of the opsonin, or, should such help be indispensable, the opsonin may be supplied by the leucocyte itself' ('Harben Lectures,' 1906).

It was in September, 1903, that Sir Almroth Wright and Captain Douglas, I.M.S., contributed to the Proceedings of the Royal Society (vol. lxxii.) their now famous paper, in which they showed by a series of experiments that the rate and activity of phagocytosis are determined by the presence in the blood-plasma of a substance which acts on the invading bacteria 'in a manner which renders them a ready prey to the phagocytes.' To this substance (which, be it observed, is quite distinct from the bacteriocides, bacteriolysins, and agglutinins) they gave the name of *opsonin* (from the Greek *ὀψωνέω* and the Latin *opsōno —I convert into palatable pabulum*), and it is distinctly to be understood that the effect they claim for it *is produced upon the bacteria* and not upon the phagocytes.

Normal blood-plasma contains opsonin, and the amount increases with every bacterial invasion. Wright further assumes that the body possesses the power of elaborating a specific opsonin for almost every kind of bacterium. It will thus be seen that, according to this view, the resisting power to bacteriogenic disease is largely determined by the quantity of the necessary opsonins which the host can provide. The blood of a patient suffering from bacterial invasion may contain an army of lusty phagocytes, and yet these may be powerless to attack the invaders. Their striking force will depend upon the extent to which the bacteria have been acted on by the opsonins. Just as the preliminary artillery bombardment in a battle, by demoralizing the enemy, prepares the way for the advance of the infantry, so do the opsonins prepare the way for the phagocytic attack.

Of the anti-bacterial elements in the blood, 'the opsonins appear to be the most important. We may ascribe to them a predominating importance, first, because it can be shown that the opsonic effect is, by either the normal or immune blood, exerted upon every species of bacteria, whereas the agglutinating effect is exerted only upon special varieties of bacteria, and the bactericidal and bacteriolytic effect among pathogenetic micro-organisms apparently only upon the typhoid bacillus and the cholera vibrio' (Wright, *Lancet*, August 17, 1907).

Not only can the presence of the opsonins in any given serum be demonstrated, but their quantity also can be estimated with remarkable accuracy.

Technique.—The method employed in order to ascertain the opsonic power of the blood is to mix together equal quantities of—

(*a*) 'Washed' leucocytes.
(*b*) An emulsion of bacteria.
(*c*) The serum containing the opsonins.

(*a*) *The 'washed' leucocytes* are obtained by taking blood from the lobe of the ear or from the finger, and passing it into a solution of 1·5 per cent. of sterile citrate of soda in normal saline (=0·75 per cent. aqueous solution of NaCl). The citrate of soda, by removing the calcium salts of the plasma, prevents clotting.

The mixture is then centrifugalized, the corpuscles thus

being made to sink to the bottom of the tube, while the liquid plasma remains above. The latter is now siphoned off, and the corpuscles again washed in normal saline. Having centrifugalized for the second time in order to sink the corpuscles, the supernatant fluid is drawn off, and the 'washed' corpuscles are then ready for use.

(*b*) *The emulsion of bacteria* is made by suspending the bacteria in normal saline solution.

(*c*) *The serum containing the opsonins* is readily procured by withdrawing blood from the lobe of the patient's ear or finger, allowing it to coagulate, and then using the expressed serum.

Equal quantities of (*a*), (*b*), and (*c*) are drawn up into a pipette and thoroughly mixed; the ends of the pipette are then sealed up in the flame, and the contents incubated at the normal temperature of the human body for twenty minutes. Films are then prepared and stained in the usual way for microscopical examination.

The Count and the Opsonic Index.—On examining such a film it will be found that a number of the bacteria have been engulfed by the leucocytes (especially by the *polymorphonuclears*), and by counting the bacteria taken up by a given number of polymorphonuclears—say fifty—an average per cell can be worked out. Suppose, for example, 450 bacteria have been counted in fifty consecutive leucocytes, then $\frac{450}{50}=9$ gives the average of engulfed bacteria per cell. Now perform an exactly similar experiment with the serum of a healthy man; then, if we suppose his count to average ten per leucocyte, the opsonic value, or, as it is usually termed, the *opsonic index*, of the patient's blood will be $\frac{9}{10}=0{\cdot}9$.

The opsonic index of a patient thus expresses the power of his opsonins to influence the ingestion of microbes by phagocytes as compared with that of the opsonins of a healthy person.

It is obvious, then, that when an individual is suffering from a bacteriogenic disease a knowledge of his opsonic index gives valuable information as to his powers of combating the disease, and that this information is essential in our endeavour to assist him by the inoculation of a bacterial vaccine.

Effect of Bacteria on the Opsonic Power of the Blood.

Wright's Law of the Ebb and Flow, Back Flow, and sustained High Tide of Immunity.—The first effect of a bacterial infection is to cause a fall in the opsonic index—the negative phase (*ebb*). This is followed by a rise to a point above its original level—the positive phase (*flow*). A second, and this time moderate, fall then occurs (*reflow*), after which the index then remains for a variable

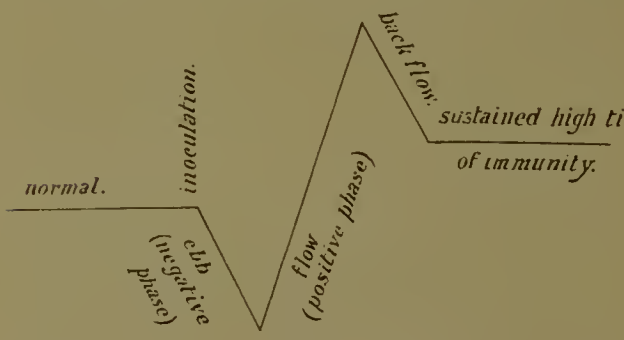


Fig. 10.

time at this higher level (*maintained high tide of immunity*).

This law holds good both for cases of ordinary bacterial infection and also for cases in which the products of dead bacteria (vaccines) are introduced into the body by inoculation.

'We have . . . during the last twelve months obtained in very numerous cases conclusive evidence of an augmentation of the opsonic power of the blood within an hour after the inoculation of tubercle vaccine, and also trustworthy witness of associated clinical improvement within that time in connection with the inoculation of tubercle vaccine in an infection of the eye' (Wright's Harvey Lecture, *Lancet*, August 24, 1907).

By a series of properly timed inoculations with the appropriate vaccines, the opsonic index of the blood can

be gradually increased to a level at which it tends to remain permanently high.

Vaccine-Therapy.

A vaccine (*vacca*, a cow) is an attenuated virus which, when introduced into the body, induces there the development of some protective substance (or substances), the effect of which is either to render the organism insusceptible to a particular disease, or to mitigate the severity of one already incurred. The protective substance on Wright's theory would be an opsonin. The vaccines in general use are watery emulsions of bacterial cultivations containing bacterial products but no living bacteria—*e.g.*, Koch's tuberculin consists of a suspension of dead tubercle bacilli.

The result of inoculation by appropriate vaccines is definitely to raise the opsonic index, and in this way to increase the capacity of the organism to resist the growth of the specific microbe.

Separate opsonins have been demonstrated for each of the following micro-organisms (Wright and Douglas, Proc. Roy. Soc., vol. lxxii., and recorded in *Lancet*, August 24, 1907):

Bacillus pulmonalis.	*Vibrio choleræ.*
Bacillus anthracis.	Gonococcus.
Bacillus pestis.	Streptococci.
Bacillus dysentericus.	Staphylococci.
Bacillus coli communis.	Pneumococci.
Bacillus typhosus.	*Micrococcus melitensis.*
Bacillus pyocyaneus.	

'*Conditions which obtain in the Case where Bacteria are Growing in, or in Contact with, Serous Effusions.*—These are well exhibited in connection with tuberculous peritonitis. Here, as my fellow-worker, Douglas, and I have already shown, the ascitic fluid has in every case a much lower opsonic index than the circulating blood. It follows that the bacteria which are cultivating themselves in, or in contact with, such ascitic fluid are not exposed to the full bacteriotropic* pressure of the circulating blood. We have here, as I have already pointed out, an explanation of the success which has attended tapping, and in particular laparotomy, in connection with tuberculous peritonitis. That success is satisfactorily accounted for by the replacement of a stagnant lymph which has forfeited much of its anti-bacterial virtue by a fluid of higher efficacy freshly derived from the circulating blood. Manifestly we should be neglecting a very im-

* 'Bacteriotropic elements' in the sense that they turn towards and enter into combination with elements of the bacterial body' (Wright).

portant element in the treatment if, while aiming at the destruction of bacteria in a serous membrane by processes of immunization, we were to fail to take into account the fact that the bacteria which are the object of our attack are cultivating themselves under a lowered bacteriotropic pressure.

'**Mixed Infections.**—Before discussing the results which have been obtained by vaccine-therapy in connection with mixed infections an introductory word may perhaps be appropriate. While the suggestion that mixed infections must be expected in suppurative processes occurring in connection with surfaces which harbour microbes may quite well be universally acceptable, as not breaking in upon any accepted belief, the suggestion that the question of mixed infection must perforce be considered in connection with every case of phthisis, lupus, tuberculous caries, tuberculous cystitis, and tuberculous ulceration, will, in the very nature of things, be unacceptable to many clinicians. Such a suggestion will be felt to call in question both the clearness of vision of those who in connection with these diseases have clamoured for anti-tuberculous remedies only, and the critical acumen of those who, without taking into account the fallacies which are incidental to clinical methods, confidently undertake to adjudicate on anti-tuberculous remedies by the observation of their clinical effects upon cases where, in addition to the tubercle bacillus, other pathogenetic microbes are at work.

'Be it acceptable or unacceptable, there is no escape from the fact that practically every case of suppurating lupus is complicated by staphylococcus infection, and that the majority of aggravated cases of lupus are complicated by a streptococcus infection. What holds true of lupus holds true, *mutatis mutandis*, of every tuberculous affection to which microbes can find access.

'Having appreciated the magnitude and the far-reaching nature of the issues involved in the treatment of mixed infections, we may come to the question of the results achieved in these cases by vaccine-therapy. We have two cases to consider.

'1. *Case where Vaccine-Therapy is directed to the Destruction of only One of the Infecting Microbes.*—In a few instances—notably in two cases where there was found in association with an atypical furunculosis a mixture of streptococci and staphylococci—the extinction of one of the microbes under the influence of the corresponding vaccine has indirectly led to the extinction of the other. This event is, however, extremely exceptional. In most cases the employment of vaccine-therapy directed to the destruction of a single species of microbe leaves the other species quite unaffected. It may even—and this applies in particular to surface infections of mucous membranes or ulcers—conduce to the multiplication of the other—*i.e.*, the originally competing microbe.

'2. *Case where Vaccine-Therapy is directed to the Destruction of all the Infecting Microbes.*—Where in cases of mixed infection measures are taken to immunize the patient against each of the different infections, very successful results have been achieved.

Successful results have been achieved notably in the case of lupus, cystitis, and endometritis. While naturally the task of the immunizator is more laborious and more intricate in the case where two or three different vaccines are employed, it would seem that the organism of the patient does not find the task of responding to a series of different vaccines (always supposing that each of these is administered in appropriate and properly interspaced doses) more difficult than the task of responding to one variety of vaccine only.

'**Generalized Infections.**—In association with my fellow-workers I have, up to the present, treated by vaccine-therapy some half-dozen cases of Malta fever, and an equal number of cases of streptococcal septicæmia. In each of the cases of Malta fever the course of the disease would seem to have been favourably influenced, the clinical improvement occurring in each case in association with an increased development of anti-bacterial substances in the blood. In the cases of streptococcal septicæmia the results have been as follows: In two cases—one of these being a case of malignant endocarditis—a complete cure was achieved, in each case in association with a very satisfactory immunizing response. In a third case—also a case of malignant endocarditis—the high temperature, which had lasted for three months before vaccine-therapy was resorted to, came down to the normal under the influence of the inoculations, the patient making an excellent immunizing response. In this case death by cardiac complication occurred in the fourth day after defervescence. In three other cases of streptococcal endocarditis the patient succumbed, having in each case failed to make any immunizing response to the inoculations' (A lecture on 'The Principles of Vaccine-Therapy,' delivered before the Harvey Society, New York, by Sir A. E. Wright, M.D., F.R.S., and recorded in the *Lancet*, August 24, 1907).

APPENDIX

MEASUREMENTS

1 metre = 39·37 English inches.
1 decimetre = 4 inches (nearly).
1 centimetre = $\frac{2}{5}$ inch (nearly).
1 millimetre = $\frac{1}{25}$ inch (nearly).
1 micromillimetre = $\frac{1}{25000}$ inch.

To convert grammes to ounces (avoirdupois) multiply by 20 and divide by 567.

To convert litres to gallons multiply by 22 and divide by 100.

To convert litres to pints multiply by 88 and divide by 50.

To convert millimetres to inches multiply by 10 and divide by 254.

To convert metres to yards multiply by 70 and divide by 64.

437·5 grains = 1 ounce.

To convert degrees Fahrenheit into degrees Centigrade subtract 32 and multiply by $\frac{5}{9}$.

To convert degrees Centigrade into degrees Fahrenheit multiply by $\frac{9}{5}$ and add 32.

INDEX

Baillière, Tindall and Cox, 8, Henrietta Street, Covent Garden

REFRACTION OF THE EYE

AND

ANOMALIES OF THE OCULAR MUSCLES.

5s. NET.

BY

KENNETH CAMPBELL, M.B., F.R.C.S.,

SURGEON TO THE WESTERN OPHTHALMIC HOSPITAL.

Lancet.—'Clearly written and gives the student all the information which . . . will enable him to treat successfully the refraction cases that he meets with.'

British Medical Journal.—'The subjects of asthenopia and anomalies of the extrinsic eye muscles are very well described and are made far simpler than is the case in some other works. The volume is well got up and illustrated, and should become popular with those who require a special book on a popular subject.'

St. Bartholomew's Hospital Journal.—'This book can be recommended as a useful introduction to the subject of refraction and various forms of squint. The subject is treated fairly fully, and the chapter on the optical principles involved is particularly lucid.'

Middlesex Hospital Journal.—'The book on the whole is good and well repays reading. . . . To advanced students and those who mean to take up eye work specially it would certainly be useful.'

London Hospital Gazette.—'A concise and clear exposition of the practical uses of the ophthalmoscope. We recommend this book to both student and practitioner.'

Dublin Medical Journal.—'. . . To those requiring a practical book on refraction of the eye, etc., the one before us will be found most valuable.'

Bristol Medical Journal.—'With this work before him no one should be at a loss to grasp the whole theory of refraction.'

Scottish Medical Journal—'. . . It is in many ways a very desirable and readable short treatise on the subject of refraction and muscular anomalies, and is worthy of the student's careful perusal.'

Pacific Medical Journal.—'An excellent little manual, written in a simple, definite, concise, and scientific manner.'

BAILLIÈRE, TINDALL & COX, 8, HENRIETTA STREET, LONDON, W.C.

To face page 176.

BAILLIÈRE, TINDALL & COX'S

SELECTED LIST OF STUDENT'S BOOKS.

THE STUDENTS' AIDS SERIES.

Specially designed to assist Students in committing to memory and grouping the subjects upon which they are to be examined.

"As aids, not substitutes, these little books afford the means of refreshing the memory, and of economising time."—*Edinburgh Med. Journal.*

Aids to the Analysis and Assay of Ores, Metals, Fuels, etc. By J. J. MORGAN, F.I.C., F.C.S. Pp. viii + 106. With eight illustrations. Price 2s. 6d. cloth ; 2s. paper.

Aids to the Analysis of Food and Drugs. By T. H. PEARMAIN and C. G. MOOR, M.A., F.C.S., Members of the Society of Public Analysts. Third edition in preparation.

Aids to Anatomy. By GEO. BROWN, M.R.C.S., and P. MACLEOD YEARSLEY, F.R.C.S. Eng. Price 2s. 6d. and 2s.

Aids to Bacteriology. By T. H. PEARMAIN and C. G. MOOR M.A. Price 3s. 6d. cloth ; 3s. paper.

Aids to Biology. By JOSEPH W. WILLIAMS
Elementary Tissues and Elementary Organisms (Protozoa and Protophyta). Second Edition. Price 2s. 6d. cloth ; 2s. paper.

Aids to Chemistry. By T. A. HENRY, D.Sc. New Edition. Price 4s. 6d. and 4s.

Aids to Practical Chemistry. By J. HURD GORDON. Price 2s. 6d. and 2s.

Aids to the Diagnosis and Treatment of the Diseases of Children. By J. McCAW, M.D., L.R.C.P. Edin. Third Edition. Price 4s. 6d. and 4s.

Aids to the Feeding and Hygiene of Infants and Children. By the same Author. Price 2s. 6d. and 2s.

Aids to Dental Anatomy and Physiology. By ARTHUR S. UNDERWOOD, M.R.C.S., L.D.S. Eng. Second Edition. Price 2s. 6d. and 2s.

Aids to Dental Surgery. By ARTHUR S. UNDERWOOD, M.R.C.S., L.D.S. Eng., and D. P. GABELL, M.R.C.S., L.R.C.P. Lond., L.D.S. Eng. Second Edition. Price 2s. 6d. and 2s.

Aids to Medical Diagnosis. By A. J. WHITING, M.D., C.M. Edin., M.R.C.S. Lond., Physician City Dispensary, Assistant Physician Tottenham Hospital. Price 2s. 6d. and 2s.

Aids to Surgical Diagnosis. By H. W. CARSON, F.R.C.S., Surgeon Tottenham Hospital. Price 3s. 6d. and 3s.

Aids to Practical Dispensing. By C. J. S. THOMPSON. Price 2s. 6d. and 2s.

Aids to Examinations ; being Questions and Answers on Materia Medica, Medicine, Midwifery, Pathology, and Forensic Medicine. By DAVID WALSH, M.B., M.Ch. Edin. Price 2s. 6d. & 2s.

Aids to Examinations. Part II. Medicine and the Allied Sciences. By T. REUELL ATKINSON, M.D. Durham. Price 2s. 6d. and 2s.

Aids to Examinations : Replies to Questions in Therapeutics. By J. BRINDLEY JAMES, M.R.C.S. Price 1s. 6d. and 1s.

Aids to Forensic Medicine and Toxicology. By WILLIAM MURRELL, M.D., F.R.C.P. Sixth Edition. 2s. 6d. and 2s.

Aids to Analytical Geometry.
I.—THE STRAIGHT LINE AND CIRCLE. By A. LE SUEUR, B.A Cantab. Second Edition. Price 2s.
II.—THE CONIC SECTIONS. By GEORGE HEPPEL, M.A. Camb. Price 2s.

Aids to Gynæcology. By ALFRED S. GUBB, M.D., M.R.C.S. D.P.H. Fourth Edition. Price 2s. 6d. and 2s.

Aids to the Mathematics of Hygiene. By R. BRUCE FERGUSON, M.A., M.D., B.C. Cantab., D.P.H., M.R.C.S. Third Edition. Price 2s. 6d. net and 2s. net.

Aids to Materia Medica and Therapeutics. By W. MURRELL, M.D., F.R.C.P. New Edition.

Part I.—Introduction and Inorganic Materia Medica. 2s. 6d. and 2s.
Part II.—Drugs of Vegetable Origin. Price 2s. 6d. and 2s.
Part III.—Synthetical Products; Drugs of Animal Origin; Glandular and Serum Therapeutics. Price 2s. 6d. and 2s.

Aids to Medicine. By NORMAN DALTON, M.D., F.R.C.P., Physician to King's College Hospital, Professor of Pathology in King's College, London.

In four parts, price 2s. 6d. and 2s. each; or in 2 vols., cloth, price 4s. 6d. each.

Aids to Obstetrics. By SAMUEL NALL, B.A., M.B. Cantab., M.R.C.P. Lond. Sixth Edition. Price 2s. 6d. and 2s.

Aids to Ophthalmic Medicine and Surgery. By JONATHAN HUTCHINSON, Jun., F.R.C.S. Third Edition. Price 2s. 6d. and 2s.

Aids to Otology. By W. R. H. STEWART, F.R.C.S.Ed. Price 2s. 6d. and 2s.

Aids to Pathology. By HARRY CAMPBELL, M.D. Lond., B.S., F.R.C.P., Lecturer at the Polyclinic, Senior Physician North-West London Hospital. Price 3s. 6d. net and 3s. net.

Aids to Practical Pharmacy. By A. CAMPBELL STARK, Demonstrator of Materia Medica and Pharmacy at St. George's Hospital, London. Price 2s. 6d. and 2s.

Aids to Physiology. Third Edition. By PEYTON BEALE, F.R.C.S. Eng., Examiner in Physiology, Society of Apothecaries, etc. 3s. 6d. and 3s. each.

Aids to Practical Physiology. By J. BRINDLEY JAMES. Price 1s. 6d. and 1s.

Aids to Physiological Chemistry. By J. L. W. THUDICHUM, M.D., F.R.C.P. Lond. Price 2s. 6d. and 2s.

Aids to Public Health. By J. L. W. THUDICHUM, M.D., F.R.C.P. Lond. Price 1s. 6d. and 1s.

Aids to Sanitary Law. By HARRY CRITCHLEY, M.A., M.D., D.P.H. Price 2s. 6d. and 2s.

Aids to Sanitary Science. By FRANCIS J. ALLAN, M.D., and R. A. FARRAR, M.A., M.D., D.P.H. Second Edition. Price 4s. 6d. and 4s.

Aids to Surgery. By JOSEPH CUNNING, M.B., B.S., F.R.C.S. Eng., Resident Medical Officer, Royal Free Hospital. Second Edition. Price 4s. net and 3s. 6d. net.

Aids to Rational Therapeutics. By J. MILNER FOTHERGILL, M.D., M.R.C.P. Lond. Price 2s. 6d. cloth; 2s. paper.

Aids to Zoology and Comparative Anatomy. By Major GREENWOOD, M.D. Price 2s. 6d. cloth; 2s. paper.

'UNIVERSITY SERIES'

OF MANUALS BY UNIVERSITY MEN FOR UNIVERSITY STUDENTS.

BUCHANAN'S ANATOMY. **Price 21s. net.**

Pp. xxvi+1562.
With 621 Illustrations, mostly original and in several colours.
(Or in 2 vols., price 25s. net.)

JELLETT'S MIDWIFERY. **Price 21s. net.**

Pp. xxiv+1176.
With 9 Plates and 467 Illustrations, plain and coloured.

LEITH'S PATHOLOGY. *In the Press.*

MONRO'S MEDICINE. **Price 15s. net.**

Second Edition. Pp. xxii+1022.
With 42 Illustrations, plain and coloured.

ROSE & CARLESS' SURGERY. **Price 21s. net.**

Sixth Edition. Pp. xiv+1350.
With 30 Plates and 500 Illustrations. (Or bound in limp leather, gilt edges, 25s. net.)

STEWART'S PHYSIOLOGY. **Price 15s. net.**

Fifth Edition. Pp. xviii+912.
With 2 coloured Plates and 395 Illustrations.

MOOR & HEWLETT'S APPLIED BACTERIOLOGY. **Price 12s. 6d. net.**

Third Edition. Pp. x+476.
With 29 plain and 73 coloured Figures.

TURNER'S MEDICAL ELECTRICITY. X-Rays, Finsen Light, Radium, and High-Frequency Currents. **Price 10s. 6d. net.**

Fourth Edition. Pp. xxiv+434. With 205 Illustrations.

MACNAUGHTON-JONES'S DISEASES OF WOMEN. **Price 21s. net.**

Ninth Edition. Pp. xl+1044.
With 122 Plates and 637 Illustrations. (Or in 2 vols., 22s. 6d. net.)

BOOKS FOR STUDENTS.

Allingham's Operative Surgery. Pp. xiv+368. With 215 original illustrations. Price 7s. 6d. net.

Elder's Ship-Surgeon's Handbook. Pp. viii + 168. Price 3s. 6d. net.

French's Medical Laboratory Methods and Tests. Second Edition, with illustrations. Price 5s. net.

Gadd's Synopsis of the British Pharmacopœia. Sixth Edition. Pp. 228. Price 1s. net.

Gant's Guide to the Examinations by the Conjoint Board, and for the Diploma of F.R.C.S. Eng., with Examination Papers. Seventh Edition. Price 5s.

Ince's Latin Grammar of Pharmacy, including the reading of Latin Prescriptions. Eighth Edition. Price 5s. net.

Lamb's Guide to the Examination of the Throat, Nose and Ear. Pp. xii+152, with 32 illustrations. Price 5s. net.

McKisack's Dictionary of Medical Diagnosis: A Treatise on the Signs and Symptoms observed in Diseased Conditions. Pp. xii+584, with 77 illustrations. Price 10s. 6d. net.

May and Worth's Manual of the Diseases of the Eye. Third Edition. Pp. viii+400, with 335 illustrations, plain and coloured. Price 10s. 6d. net.

Moorhead's Surface Anatomy. Pp. viii+150, with 23 original illustrations, plain and coloured. Price 4s. 6d. net.

Muter's Short Manual of Analytical Chemistry. Ninth Edition. Pp. xiv+236, with 56 illustrations. Price 6s. net.

Politzer's Text-Book of the Diseases of the Ear. Fourth Edition. Pp. xiv+884, with 346 original illustrations. Price 25s. net.

The Pocket Anatomy. Sixth Edition. Edited by C. H. Fagge, F.R.C.S. Pp. iv+270. Price 3s. 6d. net.

Richard's Practical Chemistry, including Simple Volumetric Analysis and Toxicology. Pp. viii+136. Price 3s. net

Scale's Elementary Microscopy. Pp. xii+180, with 78 illustrations. Price 3s. net.

Sewell's Dental Surgery. Fourth Edition. Pp. xii+622, with 281 illustrations. Price 10s. 6d. net.

Simon's Manual of Chemistry. Eighth Edition. With 9 coloured plates, and 68 other illustrations. Price 15s. net.

Sommerville's Practical Sanitary Science. Pp. x+310. With 92 original illustrations. Price 10s. 6d. net.

Walsham and Paterson's Handbook of Surgical Pathology. Third Edition. Pp. xxii+530. Price 10s. 6d. net.

BAILLIÈRE, TINDALL & COX,
8, Henrietta Street, Covent Garden, London.